VIII. *The Physiological Action of the Nitrites of the Paraffin Series, considered in connection with their Chemical Constitution.*

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Contents.

Page

Part I.

I. Introduction 505
II. Description of the Nitrites and of the Processes used in preparing them 507
III. Action of Amyl Nitrite on the Blood Pressure: Description of the Method of Investigation 514
IV. Action of other Paraffinic Nitrites on Blood Pressure contrasted with that of Amyl Nitrite 534
V. General Summary of Experiments on Blood Pressure 578
VI. General Consideration of the Modification of Nitrite Action induced by Splanchnic Stimulation and Section 583
VII. Action of Nitrites on the Human Subject 591

Part II.

VIII. Action of Nitrites on Striated Muscular Tissue: Description of the Method of Investigation 596
IX. Discussion of the Mode of Dependence of Physiological Action on Chemical Constitution 627

I.—Introduction.

The present investigation was commenced three years ago, in order to throw further light on the mode of action of the paraffinic nitrites when introduced into the animal organism, and particularly to determine in what manner this action is conditioned by the different chemical constitution of the various nitrites employed. Since the chemical constitution of these compounds is well established and their molecules are comparatively simple in structure, and moreover as their principal physiological effects are capable of accurate quantitative study, it seemed likely that the inquiry would furnish valuable pharmacological results. Although the investigation, both on its

chemical and physiological sides, has proved to be far more laborious and difficult than was anticipated, unexpected difficulties having arisen which have rendered necessary the employment of specially-devised apparatus, and the execution of several series of experiments in order to control the accuracy of the results first obtained, yet the conclusions we have finally reached will serve, we think, not only to elucidate the modes of action of these compounds, and to establish the manner of their dependence on the presence of certain groups in the respective molecules, but we hope may also be of some importance in their bearings on the treatment of disease. It is already known that the physiological action of amyl and ethyl nitrites closely resembles in its important features that of the metallic nitrites, and that the characteristic effect is due to the presence in both series of compounds of the nitroxyl group NO_2, the nitrogen of this group not being directly united to the metal or organic radical, but indirectly by means of an atom of oxygen (R'ONO). Our knowledge of the physiological behaviour of the organic nitrites has been almost wholly derived from the study of amyl nitrite, which has been observed to produce a similar, but far greater, effect than its lower homologue, ethyl nitrite, whose action, however, has not hitherto been so closely examined as that of the amyl compound. Both these organic nitrites are therapeutically employed, the amyl compound at the suggestion of LAUDER BRUNTON, who proposed to use it in the treatment of certain diseases on account of its known physiological action. Unfortunately, however, it seems likely that most of the results which have been obtained with amyl nitrite are to a large extent vitiated by the circumstance that, as a rule, sufficient pains have not been taken to procure the nitrite in a chemically pure state.

One of us has already shown* that the material usually employed in medicine under the name of amyl nitrite is highly impure, containing a large proportion of other nitrites (ethyl, propyl, butyl), as well as their oxidation products. The redistilled amyl nitrite which has been employed by some investigators is a mixture of two amyl nitrites with a variable proportion of iso-butyl nitrite. In the present investigation special precautions were taken to obtain the various nitrites in a pure state. The compounds selected for examination were: methyl nitrite, ethyl nitrite, primary propyl nitrite, secondary propyl nitrite, primary butyl nitrite, iso-butyl nitrite, secondary butyl nitrite, tertiary butyl nitrite, α-iso-amyl nitrite, β-iso-amyl nitrite, tertiary amyl nitrite. These nitrites were chosen because they contain nitroxyl united to typical and differently constituted radicals. Their examination would, therefore, enable us to determine the modifying influence exerted by these radicals upon the characteristic action of nitroxyl.

Having concluded a complete investigation of the physiological action of these nitrites, we found that many of the results we had obtained were so remarkable, and in some respects contrary to what *primâ facie* seemed probable, that we determined

* DUNSTAN and WOOLLEY, "On the Constituents of the Amyl Nitrites used in Medicine." 'Pharm. Journ.' (3), vol. 19, p. 487.

to repeat all the most important experiments. This necessitated the preparation of fresh specimens of all the compounds.

After spending nearly the whole of the past year in this work of verification we had the great satisfaction of obtaining entire confirmation of our original results. In no instance was any important difference detected in the behaviour of these bodies.

In this, the first part of our communication, we shall give a short account of the principal work which has already been done on the subject, and shall then proceed to describe the methods by which the nitrites have been prepared and their purity ascertained. Of the numerous physiological experiments that have been made, we have selected for description such as are best suited to emphasize the peculiarities in the behaviour of these bodies. The physiological actions which we have made the subject of special study are those on blood pressure, pulse, and respiration, whilst we have also fully examined the action on striated muscular fibre. The first portion of the paper (Secs. III.–VII.) will deal almost entirely with the action of the various nitrites on blood pressure, and with the special apparatus used in its study. The latter part (Sec. VIII.) of the paper will have reference to the action of these same nitrites in producing contraction of striated muscle, and will conclude with a chemical discussion of the whole of our results.

The chemical part of this inquiry has been conducted in the Research Laboratory of the Pharmaceutical Society, and the physiological portion in the Pharmacological Laboratory of the University of Aberdeen.

The expenses of the research have been in part defrayed by grants made by the Royal Society and by the Scientific Grants Committee of the British Medical Association.

II.—Description of the Nitrites and of the Processes used in Preparing them.

The nitrites have been prepared by a process which has already been described, so far as it relates to the production of ethyl, iso-butyl, and amyl nitrites.* It consists in acting in the cold with dilute sulphuric acid and an excess of sodium nitrite on the corresponding alcohol previously obtained perfectly pure ($R'OH + HNO_2 = R'NO_2 + H_2O$). The alcohol is mixed with the well-cooled solution of sodium nitrite, and the dilute sulphuric acid gradually added; in some cases a mixture of the alcohol and acid is gradually added to the excess of sodium nitrite in aqueous solution. This has proved to be a satisfactory method for preparing the entire series of paraffinic nitrites with which we have worked. When secondary and tertiary alcohols have been used, it has been found desirable to employ acetic acid instead of sulphuric acid to bring about the reaction. The liquid nitrites, after having been thoroughly washed and

* Dunstan and Dymond, "On the Preparation of Ethyl Nitrite." 'Pharm. Journ.' (3), vol. 19. Dunstan and Woolley, "On Iso-butyl Nitrite." 'Pharm. Journ.' (3), vol. 19, p. 487. Dunstan and Williams, "On the Metameric Amyl Nitrites." 'Pharm. Journ.' (3), vol. 19, p. 488.

dried, were repeatedly distilled, sometimes under reduced pressure, until a liquid boiling at a constant temperature was obtained. That the liquids thus obtained had the composition of the required nitrites was proved by determining the amount of iodine liberated by each compound from an acid solution of potassium iodide in the absence of oxygen, the operation being conducted in an apparatus specially devised for the purpose which has already been described.* In every case the precaution was taken of determining the physiological action of the nitrites almost immediately after their preparation, since most of these bodies suffer some decomposition when kept. The purity of each nitrite was thus ensured (1) by the employment of the pure alcohol in the first instance; (2) by the distillation of the liquid at a constant temperature; (3) by the results of a particularly delicate process of analysis. The composition of each nitrite was in this way determined with greater accuracy than would have been possible by the usual method of determining the amount of nitrogen by combustion.

The following are the names, formulæ, and boiling-points of the nitrites with which we have worked :—

Name.	Formula.	Boiling-point.
Methyl nitrite	CH_3NO_2	Gas (12°)
Ethyl nitrite	$CH_3CH_2NO_2$	17°
Primary propyl nitrite	$CH_3CH_2CH_2NO_2$	48°
Secondary propyl nitrite	$(CH_3)_2CHNO_2$	39°·5
Primary butyl nitrite	$C_2H_5CH_2CH_2NO_2$	76°
Secondary butyl nitrite	$C_2H_5CH_3CHNO_2$	68°·5
Tertiary butyl nitrite	$(CH_3)_3CNO_2$	63°
Iso-primary butyl nitrite	$CH_3CH(CH_3)CH_2NO_2$	67°
α-iso-primary amyl nitrite	$CH(CH_3)_2CH_2CH_2NO_2$	97°
β-iso-primary amyl nitrite†	$C_2H_5CH(CH_3)CH_2NO_2$	95°–96°
Tertiary amyl nitrite	$C_2H_5(CH_3)_2CNO_2$	92°

Certain of these nitrites were prepared by us for the first time,‡ whilst of those previously described some have been found to possess physical properties differing from those usually ascribed to them. For the purpose of administration a known volume of each nitrite was taken, and in the description of the experiments the weight corresponding to the volume is given in brackets, as well as the weight of nitroxyl (NO_2) contained in the quantity of the substance administered, this weight being calculated from the molecular weight and the relative density of the compound.

The preparation, purification, and analysis of these nitrites has been a most laborious and tedious undertaking, and we wish to express our great indebtedness to

* Dunstan and Dymond, "On an Apparatus for the Estimation of Nitrites." 'Pharm. Journ.' (3), vol. 20.

† These two amyl nitrites are subsequently called for shortness α-amyl and β-amyl respectively.

‡ Some of them have since been prepared by Bertoni.

Miss Lucy Everest Boole for the able assistance she has rendered us in carrying out this work.

Methyl Nitrite, CH_3NO_2.—This nitrite, which is a gas at ordinary temperatures, was prepared by the reaction of aqueous sodium nitrite and pure methyl alcohol with dilute sulphuric acid. The quantities used were calculated from the chemical equation, the sodium nitrite being employed in slight excess. The alcohol and the acid were each diluted with an equal volume of water, and, after having been well cooled, were gradually mixed. This mixture was allowed to slowly drop from a tap-funnel into a solution of sodium nitrite (made by dissolving the salt in about three times its weight in water) contained in a flask cooled by water. Methyl nitrite was immediately formed and passed forward into a U-tube filled with quicklime cooled by ice. In this way the gas was freed from acid vapour and from water. It was found, however, on analysis, to be contaminated with small quantities of nitric oxide. In order to obtain it free from this impurity the gas, on emerging from the U-tube, was conducted into well cooled methyl alcohol until the liquid was completely saturated. On warming this solution methyl nitrite was copiously evolved. The gas was freed from the accompanying vapour of methyl alcohol by passing it through the U-tubes, containing porous calcium chloride cooled to 0°. For the purpose of analysis some of the gas was collected in a gas analysis apparatus over dry mercury, and from thence a known volume was introduced into the apparatus in which its iodine liberating power was ascertained.

The results of the analysis showed the gas thus prepared to be pure methyl nitrite (weight of methyl nitrite, corresponding to the volume taken, = 0·0951 grm.; weight of methyl nitrite, calculated from iodine liberated, = 0·0953 grm.). The gas was collected in thin glass bulbs of known capacity (2–10 cub. centims.), a series of such bulbs being connected with the generating and drying apparatus above described, and a current of gas passed through until the whole of the air was completely expelled, as evidenced by the entire absorption of the escaping gas in well-cooled methyl alcohol. The last bulb of the series was provided with a fine extremity, which dipped into the cooled alcohol. As soon as the minute bubbles of escaping gas were completely absorbed the two ends of each bulb were quickly sealed with a small flame. The temperature and pressure having been observed during the process, the weight of methyl nitrite contained in each bulb was readily calculated, and, in order to be quite certain that the proper quantity of methyl nitrite was actually present, one or two of the bulbs selected from each series were broken and the quantity of contained nitrite estimated by analysis.

Ethyl Nitrite, $C_2H_5NO_2$.—The method of preparing this compound in a pure state has already been described in a previous paper.* A mixture of dilute sulphuric acid and pure ethyl alcohol was caused to react at a low temperature with a solution of sodium nitrite. The sodium nitrite solution having been cooled to 0°, the mixture of

* Dunstan and Dymond, "On the Preparation of Ethyl Nitrite," 'Pharm. Journ.' (3), vol. 19, p. 7.

dilute acid and alcohol is gradually introduced through a thistle funnel to the bottom of the cold solution of the salt. Under these circumstances there rises to the surface the pale yellow liquid nitrite, which is washed, dried (with potassium carbonate), and distilled. The sodium nitrite is employed in slight excess to prevent the nitrite from coming into contact with dilute sulphuric acid, which readily decomposes it. The pure liquid boils at 17° (barometric pressure, 760 millims.), and its relative density is 0·900 at 15°/15°.

Primary Propyl Nitrite, $C_2H_5CH_2NO_2$.—This compound was prepared by the reaction of a mixture of sulphuric acid and pure primary propyl alcohol with aqueous sodium nitrite, the operation being conducted as in the preparation of the ethyl compound. The quantities taken were calculated from the equation, the sodium nitrite being used in slight excess. The greater part of the liquid distilled constantly at 48° (barometric pressure, 761·8 millims.). Its relative density was 0·895 at 15°/15°. Analysis proved it to be propyl nitrite: the nitrite was weighed into propyl alcohol, and the iodine-liberating power of the liquid ascertained. (Weight of propyl nitrite taken, 0·2062 grm.; weight of propyl nitrite calculated from the amount of iodine liberated, 0·2063 grm.).

The physical constants usually assigned to this compound differ very considerably from those we have found for the liquid prepared as above described. Its discoverer, Cahours ('Comptes Rend.,' vol. 77, p. 745), states that it boils between 43° and 46°; its relative density at 21° being 0·935. Přibram and Handl ('Monatshefte' 2, p. 655) have recorded 53°–60° (barometric pressure, 736 millims.) as the boiling-point, and 0·9981 as the relative density at 0°. More recently Bertoni and Truffi ('Gazz. Chim. Ital.,' vol. 14, p. 23) have obtained primary propyl nitrite by acting on iso-amyl nitrite with primary propyl alcohol. They state that it boils at 57°.

In order to obtain confirmatory evidence of the correctness of our results, the nitrite was prepared by an entirely distinct method, viz., by the reaction of primary propyl iodide with silver nitrite. The resulting mixture of primary propyl nitrite and primary nitropropane was fractionally distilled. By this means the nitrite was obtained, and found to correspond exactly with that we had prepared from the alcohol as above described.

Secondary Propyl Nitrite, $CH_3CH_2CHNO_2$.—This nitrite was obtained by acting on pure secondary propyl alcohol with dilute sulphuric acid and solution of sodium nitrite, the details of the method being similar to those described in connection with ethyl nitrite. A liquid was obtained which boiled constantly at 39°·5 (barometric pressure, 752 millims.). Its relative density was 15°/15° 0·871. Analysis proved it to be secondary propyl nitrite. (Weight of nitrite taken dissolved in the alcohol, 0·1899 grm.; weight of nitrite calculated from the amount of iodine liberated, 0·190 grm.) According to Silva ('Bull. Soc. Chim.,' vol. 12, p. 227) secondary propyl nitrite boils at 45°, whilst Kissel ('J. Russ. Chem. Soc.,' vol. 14, p. 229) alleges that another modification is formed by the reaction of secondary propyl iodide with silver

nitrite, which boils at about the same temperature, but more closely resembles a nitro-compound than a nitrite. Owing to these discrepant statements we determined to compare the properties of the nitrite resulting from the reaction of the iodide and silver nitrite with those of the nitrite we had obtained. Pure secondary propyl iodide was caused to react with dry silver nitrite, the operation being conducted in a manner described by one of us in a previous paper on the reaction between ethyl iodide and silver nitrite.*

A liquid was obtained which boiled constantly at 39°·5, and corresponded exactly with the nitrite we had obtained from the alcohol.

Nothing else could be obtained from the original liquid except secondary nitropropane. No trace of any such substance as that described by KISSEL could be isolated.

Primary Butyl Nitrite, $C_2H_5CH_2CH_2NO_2$.—This nitrite was prepared by the reaction of a mixture of pure primary butyl alcohol and dilute sulphuric acid, with a slight excess of solution of sodium nitrite. The details of the operation are precisely similar to those followed in the preparation of the nitrites previously described. A large quantity of a pale yellow liquid was obtained, which distilled constantly between 75°–76° (barometrical pressure, 757 millims.). It was identified as primary butyl nitrite by estimating the amount of nitrous group contained in a weighed quantity of the liquid dissolved in butyl alcohol (weight of nitrite taken, 0·1513 grm., weight of nitrite calculated from the amount of iodine liberated, 0·1512 grm.). Its relative density was 0·891 at 15°/15°. This nitrite is one of the most unstable of those prepared. It was found impossible to keep it unchanged for any length of time. It has been prepared by BERTONI ('Gazz. Chim. Ital.,' vol. 18, p. 434) by acting on glyceryl trinitrite with primary butyl alcohol. He states that it boils at 75°, and has at 0° a relative density of 0·911.

Secondary Butyl Nitrite, $C_2H_5CH_3CHNO_2$.—We attempted to prepare this nitrite by the reaction of pure secondary butyl alcohol (obtained by the reduction of ethyl methyl ketone), with dilute sulphuric acid and excess of sodium nitrite. It was found difficult by this method to obtain any considerable quantity of liquid distilling at a constant temperature. A more abundant product resulted from the substitution of strong acetic acid for dilute sulphuric acid and the use of less water to dissolve the sodium nitrite, but under these circumstances the reaction is much slower. The secondary nitrite thus prepared boils at 68°·5 with some decomposition. Its relative density at 15°/15° was 0·874. Its analysis proved it to be secondary butyl nitrite (weight of nitrite taken 0·1602 grm., weight of nitrite calculated from the amount of iodine liberated, 0·1587 grm.). BERTONI ('Gazz. Chim. Ital.,' vol. 18, p. 435) has recently prepared this nitrite by acting on glyceryl trinitrite with secondary butyl alcohol. He found its boiling point to be 68°, and its relative density at 0°, 0·898.

† DUNSTAN and DYMOND, "On the Alleged Existence of a Second Nitro-ethane," 'Chem. Soc. Journ.,' 1889.

Tertiary Butyl Nitrite, $(CH_3)_2CNO_2$.—This nitrite was found to be best prepared by the modification of the general process described in connection with secondary butyl nitrite, acetic acid being substituted for dilute sulphuric acid. By this means a yellow liquid was obtained which boiled with slight decomposition at 63° (barometrical pressure, 760 millims.). In purifying it, distillation under reduced pressure was resorted to. Its relative density was found to be 0·8715 at 15°/15°. The compound when analysed yielded the following result (weight of nitrite taken dissolved in the alcohol, 0·203; weight of nitrite calculated from the amount of iodine liberated, 0·205). This nitrite was first obtained by TSCHERNIAK ('LIEBIG'S Ann.,' vol. 180, p. 155), by acting on silver nitrite with tertiary butyl iodide. He states that it boils at 76°–78°. The correctness of our results with this nitrite have been confirmed by those obtained by BERTONI ('Gazz. Chim. Ital.,' vol. 15, p. 358), who prepared the compound by the interaction of glyceryl trinitrite with tertiary butyl alcohol. The resulting liquid boiled at 62°–63°, and its relative density at 0° was 0·8941. There can therefore be no doubt that the higher boiling-point recorded by TSCHERNIAK was due to the nitrite having been contaminated with the corresponding nitro-compound which was formed simultaneously.

Iso-Butyl Nitrite, $CH_3CH(CH_3)CH_2NO_2$.—The mode of preparing this nitrite by the reaction of pure iso-butyl alcohol, dilute sulphuric acid, and sodium nitrite has already been described by one of us.* A large yield of the pure substance is readily obtained. It boils at 67° (barometric pressure, 760 millims.), and its relative density at 15°/15° is 0·876. When analysed it afforded the following result (weight of nitrite taken, 0·1513 grm.; weight of nitrite calculated from the amount of iodine liberated, 0·1512 grm.). BERTONI ('Gazz.,' vol. 14, p. 23) records 66°–67° as the boiling point of this nitrite.

α-Amyl Nitrite, $CH(CH_3)_2CH_2CH_2NO_2$.—This nitrite was first prepared in a pure state and described by one of us in 1888.† The pure α-amyl alcohol or iso-butyl carbinol, the optically inactive amyl alcohol of fusel oil, was separated from the mixture of α-amyl alcohol and β-amyl alcohol (fusel oil) by PASTEUR'S method of repeatedly crystallizing the two barium amyl sulphates. The process was a most laborious one, necessitating the recrystallization of the barium salts from water thirty-four times in succession, in order to completely remove the more soluble salt corresponding to β-amyl alcohol, the optically active alcohol of fusel oil. The nitrite was prepared by reaction with sulphuric acid and sodium nitrite. The compound distilled constantly at 97° (barometric pressure, 758·5 millims.). The relative density at 15°/15° is 0·880. Analysis showed the liquid to possess the composition of α-amyl nitrite (weight of nitrite taken 0·178 grm.; weight of nitrite calculated from the amount of iodine liberated 0·179 grm.).

β-Amyl Nitrite, $C_2H_5CH(CH_3)CH_2NO_2$.—This nitrite which corresponds to β-amyl

* DUNSTAN and WOOLLEY, "On Iso-Butyl Nitrite." 'Pharm. Journ.' (3) vol. 19, p. 487.

† DUNSTAN and WILLIAMS, "On the Metameric Amyl Nitrites." 'Pharm. Journ.' (3), vol. 19, p. 488.

alcohol or secondary butyl carbinol the optically active alcohol of fusel oil was not isolated in an absolutely pure state. Its physiological action was ascertained by examining the nitrites prepared from a mixture in known proportions (calculated from the rotatory power of the mixture of β-amyl alcohol and α-amyl alcohol) the physiological action of the α-amyl nitrite having been previously ascertained. It is doubtful whether pure β-amyl alcohol has yet been obtained, since the numbers representing the optical activities of specimens prepared by different observers are very discordant. For the purposes of our calculations, we have adopted the number found by LE BEL, whose alcohol produced a greater rotation than that of any other observer ($\alpha_D = 4° 58'$).

We have found that the nitrite prepared from this lævo-rotatory alcohol by the action of dilute sulphuric acid and sodium nitrite is dextro-rotatory. The nitrite boils between 95°–96°, and appears to possess a smaller relative density than the α-nitrite.

Tertiary Amyl Nitrite, $C_2H_5(CH_3)_2CNO_2$.—An attempt was made to prepare this nitrite by the interaction of the pure alcohol with dilute sulphuric acid and sodium nitrite. The reaction was extremely violent, even at a low temperature, and only a very small yield of a homogeneous liquid was obtained. By repeating the process and substituting strong acetic acid for dilute sulphuric acid a much better result was obtained. The alcohol was mixed with a solution of sodium nitrite dissolved in the necessary quantity of water, and the strong acetic acid (glacial acetic acid diluted with half its volume of water) gradually added. The reaction occurred slowly, and in order to facilitate it the mixture was transferred to a bottle and well shaken. The yellow layer of nitrite was then decanted and washed. The substance was observed to be decomposed by prolonged contact with water or by digestion with potassium carbonate, which therefore could not be used to dry it. To remove traces of acid from the liquid, a small fragment of calcium hydroxide was added, and to remove water the liquid was digested with anhydrous calcium nitrate. On distilling it under reduced pressure, a large quantity of liquid was obtained between 30°–31°; under atmospheric pressure the nitrite boiled at 92°, with some decomposition. Its relative density was 0·890 at 15°/15°. Analysis showed that the composition of this liquid corresponded with the formula of tertiary amyl nitrite (weight of nitrite taken, 0·184 grm.; weight of nitrite calculated from the amount of iodine liberated, 0·182 grm.). Tertiary amyl nitrite is one of the most difficult of the series to obtain pure, and it cannot be kept without suffering decomposition. BERTONI ('Gazz. Chim. Ital.,' 16, 515) has recently prepared this compound by acting on tertiary amyl alcohol with glyceryl trinitrite. He states that it boils at 92°–93°, and has at 0° a relative density of 0·903.

III.—Action of Amyl Nitrite on the Blood Pressure. Description of the Method of Investigation.

The large amount of attention which has been bestowed on the action of nitrite of amyl during the last thirty years, has established certain facts regarding it which are recognised on all hands; but it has left us in considerable doubt as to the occurrence of other phenomena which are described by some investigators, but questioned by others. The explanation of even the most evident nitrite effect, viz., the fall of blood pressure, is still disputed.

The principle observed in the experiments, which it seemed advisable to make, in order to obtain further information on the action of nitrates, has been to carefully analyse and contrast the effect produced by exactly measured quantities of the pure bodies upon the whole organism, or certain of its tissues.

After briefly sketching the history of previous investigations with the so-called amyl nitrite, in so far as they bear upon the scope of our inquiry, the action of pure nitrite of amyl will be discussed in detail, in order that its effects may serve as a basis for contrast with the bodies which will be considered in a later portion of this paper.

History.

Nitrite of amyl, discovered in 1844 by Balard,* was examined in 1859 by Guthrie,† who showed that its inhalation was followed by reddening of the face, and acceleration with alteration in form of the pulse. Richardson‡ confirmed the occurrence of capillary dilatation (68); Gamgee§ observed a fall in the blood-pressure, and, in 1873, Aurez Droz measured it; Brunton,‖ in 1871, endeavoured to show that the seat of direct action of the drug is in the walls of the vessels, and observed that vagotomy increased its effect. Filehne¶ opposed Brunton's view, and regarded the action as primarily central.

Amongst those who have supported Brunton's views are Pick,** Wood,†† Mayer,‡‡ and Friedrich.§§ Aurez Droz,‖‖ it is true, localises the nitrite action at the periphery, but refers it to the nerve terminations there. On the other hand,

* 'Ann. d. Phys. Nml. et Path.,' 1873.
† 'Ann. d. Chem. et Pharm.,' v. 3.
‡ 'Trans. Brit. Med. Assoc.,' 1864–72.
§ 'Phil. Trans.,' 1868.
‖ 'Journ. of Anat. and Phys.,' v. 5.
¶ Pflüger's 'Arch.,' v. 9, p. 471.
** 'C.-Blatt. Med. Wis.,' 1873, p. 865.
†† 'Amer. Journ. Med. Sci.,' July, 1871.
‡‡ 'Arch. f. Exp. Path. u. Pharm.,' v. 5, 63.
§§ 'Arch. f. Exp. Path. u. Pharm.,' v. 5, 76.
‖‖ 'Arch. d. Phys.,' 1873, p. 407.

FILEHNE is in part supported by BERNHEIM, GUTTMANN, MCBRIDE, and KEMPTON in his contention that the first effect of the drug is a central nervous paralysis.

The "capillary dilatation" (as it is usually designated by authors) was especially studied by RICHARDSON and by MAX SCHÜLLER in the pia mater, by GASPY in the rabbit's ear, by AUREZ DROZ in the swim-membrane of the frog; but it was not recognised locally by GAMGEE and MCBRIDE* when observing the forearm or leg. FILEHNE saw no reddening of the lungs; and PICK failed to detect retinal pulsation under nitrite action.

A slowing of respiration followed by acceleration with diminution of thoracic movement was observed by VERGRIERES, BOURNEVILLE,† and CRICHTON BROWNE.

An acceleration of the heart of animals was seen by almost all experimenters, including WOOD, who stated that nitrite of amyl accelerated the heart by direct action, whilst others attributed the change to suspension of vagus tonus. But these observations were questioned by FILEHNE, who pointed out that in frogs and other animals to which the nitrite had been repeatedly given, slowing of the heart was produced.

The poisonous action of the nitrite of amyl upon muscle is mentioned by WOOD—who recognized it as a paralysant both in the fluid and vaporous form,—by BRUNTON with GRESSWELL,‡ and by PICK,§ the last of whom exposed curarised muscles to nitrite of amyl vapour, and found that they completely lost excitability; whilst spinal paralysis is described by WOOD, convulsions by BRUNTON and others.

BRUNTON, GAMGEE, HAY,‖ GIACOSA,¶ JOLYET, and REYMOND,** with others, discuss the chemical changes produced in the blood by nitrite action. The reduction of body temperature has been widely recognized by experimenters as a nitrite effect.

Amongst those who have, by clinical study, extended our knowledge concerning the action of nitrite of amyl, need only be mentioned here: LAUDER BRUNTON, who showed its curative effects in angina pectoris; WEIR MITCHELL,†† who wrote upon its favourable effects in epilepsy; Drs. CRICHTON BROWNE and BOURNEVILLE,‡‡ who made observations in the same direction; and ANSTIE, who employed it in gastric spasm.

The names of RICHARDSON, TALFOURD JONES, RINGER with MURRELL and MACCULLOCH, must also be remembered in connection with the investigation of the

* 'Chicago Journ. of Nerv. and Mental Dis.,' 1875.
† 'Gaz. Méd. d. Paris,' 1876, p. 150.
‡ 'St. Barts. Hosp. Reports,' 1876, p. 143.
§ 'Centralbl. d. Med. Wis.,' Berlin, 1873.
‖ 'Practitioner,' June, 1883.
¶ 'Zeitsch. f. Physiol. Chem.,' vol. 3, p. 54.
** 'Gaz. Méd. de Paris,' 1875.
†† 'Phil. Med. Times,' 1872, p. 353.
‡‡ 'Gaz. Méd. de Paris,' 1876.

therapeutical and antidotal action of this drug or its allies, whilst the important and most recent contributions on ethyl nitrite by LEACH and by FRASER must be borne in mind, as illustrating the therapeutic value of these compounds.

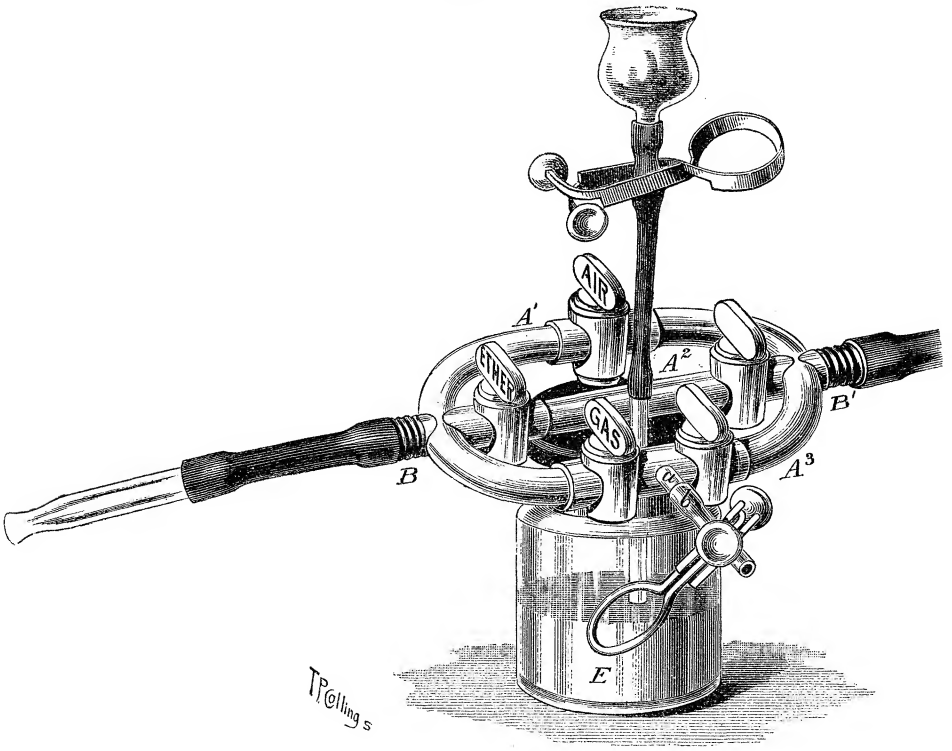
Methods Employed in the Investigation.

The difficulty in following exactly the results obtained by many observers who have experimented upon the action of nitrites, is owing not only to the doubtful purity of the nitrite employed, but partly also to the scanty idea conveyed as to the actual amount inhaled by the individual or animal experimented upon.

Supposing that, according to the usual custom, "a few drops" have been poured upon some fabric, and held near the mouth and nose; it would follow that, according to the actual distance of the drug from the face, the activity of respiration, the temperature of the room, and the volatility of the nitrite employed, a larger or smaller amount (we can hardly say approximately how much) would be inhaled and produce the various effects upon respiration, heart, and peripheral vessels, and even upon the central nervous system, which are recorded as nitrite effects. In order to obviate such discrepancies as must arise from want of uniformity in the dose, a special apparatus was used in this research for administering nitrites by inhalation through the nostrils in the human subject, and another for administration through the trachea in animals. The former will be described in a subsequent section. The latter (fig. 1) consisted of three short tubes, A^1, A^2, A^3, of equal diameter, somewhat greater than the trachea of a large cat, permanently connected by means of two common or main tubes (B and B^1) to which they converged at their ends. One of the three tubes (A^1) had no further connection; the second (A^2) passed through the stopper of the ether bottle (E) without dipping (somewhat as in BRUNTON'S special apparatus for administration of anæsthetics); the third (A^3) resembled the first, but had a smaller brass tube (a) introduced at a right-angle. Two stop-cocks, one on either side of (a), were placed in the course of the large tube A^3. Through the tube A, when provided with a continuation of india-rubber (b) and a clamp, the nitrite could be discharged from the graduated pipette, a small fraction of a minim of water being introduced behind it to insure its entire washing out. In the greater number of experiments, instead of introducing the nitrite directly through the lateral tube into the partition between the stop-cocks, a spindle-shaped bulb, closed by tubing clamped at each end, was brought into connection with it, the nitrite having been previously introduced into the bulb. In the nitrite of methyl experiments, in which the body was in a gaseous state, the same plan was followed, the hermetically sealed ends of the bulb being broken before the stop-cock giving access to the tracheal cannula was opened. Distal to the bulb in all cases was a water valve which permitted ingress but not egress of air. A similar valve was placed in connection with the common tube B. The tracheal cannula was

provided laterally with a valve permitting exit but not entrance of air. When all the stop-cocks in the apparatus (fig. 1) were closed, with the exception of the one nearest the animal in tube A^3, and the clamps on the bulb were unscrewed, the whole of the nitrite was inhaled, the water valve preventing loss upon expiration. For the continued administration of the anæsthetics it was usually found sufficient to have the air tube partially and the ether tube fully open, so that inhalation could take place through both of them simultaneously. The adjustment to produce steady but not excessive etherisation was made before the experiment commenced, and was usually adhered to throughout.

Fig. 1.



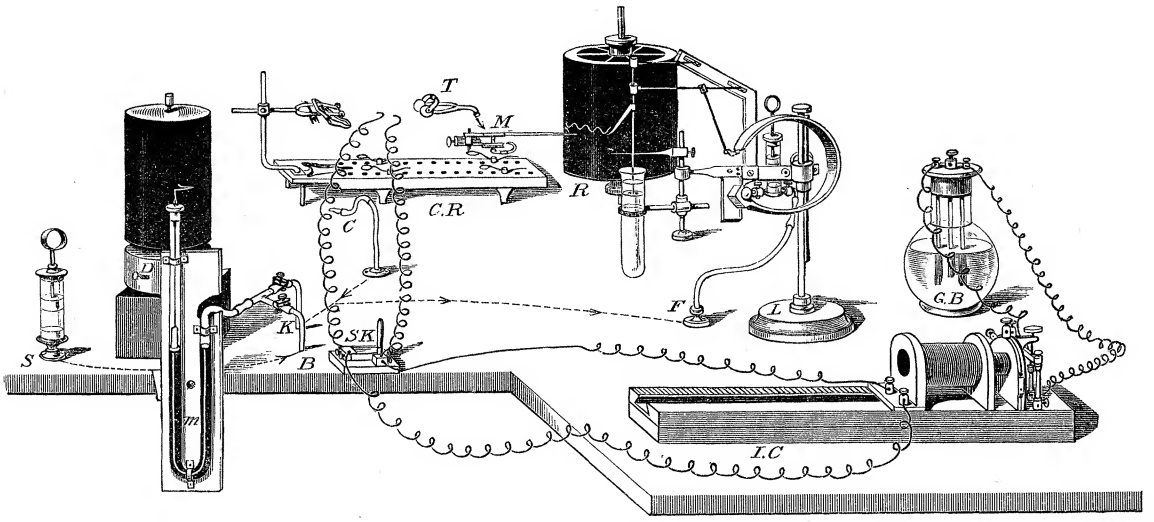
Apparatus for administration of an anæsthetic or other volatile bodies (one-half actual size). For description, see text.

At the moment of nitrite inhalation, the first intermediate tube (A^1), which was used for air supply alone, as well as the proximal ether tube (A^2), were turned off, and the nitrite tube (A^3) opened. The special valvular arrangement which has been described did not permit the expired air to return to the tube apparatus, so that there was no loss of the nitrite during expiration, and practically the whole amount entered the trachea.

Absolutely exact measurements of the nitrite were made by means of fine capillary glass pipettes, very carefully graduated. The bulk was thus ascertained, and the weight subsequently determined from the relative density. One pipette was used

for a given dose throughout an experiment; it was thoroughly cleansed between every two measurements by washing with water, then with alcohol, and finally drying by heat. The recording apparatus (fig. 2) for the blood-pressure was arranged much in the same way as in experiments made conjointly by Dr. LAUDER BRUNTON and one of us. (C.) It consisted of a mercurial manometer writing upon a slowly revolving drum (one revolution in one hour), and a Fick's kymograph, writing upon a more rapidly revolving Balzar's cylinder. These manometers could be employed separately by clamping one of them off, but as a rule, when only pressure and number of pulsations were being observed, both were kept open. The advantage of this arrangement is that a considerable period of time is represented by a short lineal movement on a small drum, while on the quick cylinder the pulse can be reckoned, and the course of the rapidly occurring variations of pressure studied.

Fig. 2.



Arrangement of apparatus used in blood-pressure experiments (partly diagrammatic). For description see text.

Respiration was recorded on the rapid cylinder by a registering Marey's tambour, attached to a double tambour placed upon the thorax of the animal. An electrical signal in connection with a key and Daniell's element was placed beneath the point recording the blood-pressure, in order to mark the time of administration of nitrites, &c. For the purpose of simplifying the apparatus in some experiments, the marking was done manually by an assistant, whose entire charge it was.

When vagus, splanchnic, or sciatic stimulation was employed, a double key admitted the Faradic current from the secondary coil of a Du Bois-Reymond's inductorium to the electrodes under the nerve, and at the same time it closed the signal circuit, and thus indicated the length of stimulation. Natural respiration was allowed to continue so long as it was unimpaired, but to secure regular volatilization

of the nitrite, artificial respiration was substituted whenever the respiration became distinctly abnormal. It was also, of course, employed when preparation of the splanchnic nerves in the thorax necessitated resection of the ribs.

The course of a simple nitrite administration was the following:—When the blood-pressure was steady, the clockwork of the big drum was started, to bring it up to full speed before the cylinder was caused to rotate, by screwing up the friction wheel. The nitrite was then introduced into the side tube (fig. 1) of the inhaler, or into the bulb connected with this tube, both of the stop-cocks on A^3 and the clamp on *b* being closed. The cylinder was then started, and after a sufficient record of the pulse and respiration had been taken, the nitrite was given, the time of administration being recorded. During administration the tube A^2 was usually closed. After a sufficient time had been allowed for its inhalation (complete volatilization of the small amounts of the nitrite employed was found to take place in a very few inspirations), the air and ether tubes, if these had been closed, were re-opened, and the quick drum permitted to run as long as necessary for obtaining a full record of the changes in pulse and pressure. During the subsequent recovery of pressure, an occasional record of pulse and respiration was taken on the quick drum; corresponding marks being made on the slow drum.

Action of α-Amyl Nitrite on Blood-Pressure.

On all hands it is admitted that moderate doses of the nitrites hitherto examined cause a fall of blood-pressure, resulting chiefly, if not entirely, from a marked dilatation of the arterioles greatly reducing the peripheral resistance.

In explaining the cause of this dilatation, a divergence of opinion is observable. FILEHNE may be considered the chief authority who has striven to demonstrate experimentally that they act on the vaso-motor centre or centres. On the other hand, BRUNTON and MAYER with FRIEDRICH* maintain that their chief action is direct, on the walls of the vessels, and does not depend on a central effect. MAYER and FRIEDRICH by using the manometer found in the rabbit (1) that when the circulation was cut off from the brain and artificial respiration maintained, the blood-pressure still sank during inhalation of amyl nitrite; and (2) that when it had access to the brain alone, no fall of pressure ensued.

FILEHNE,† experimenting upon rabbits, and observing the dilatation of the auricular vessels as indicating the action of the drug, arrived at the following chief results:—(1) That if the sympathetic nerve be cut on one side of the neck, and then stimulated by an interrupted current so as to maintain a normal degree of vascular contraction in the ear, the nitrite does not produce vascular dilatation on that, but on the other side. (2) If the vessels of one ear are isolated and artificial circulation

* MAYER, FRIEDRICH: 'Archiv f. Exp. Path. und Phys.,' vol. 5, p. 76.

† FILEHNE, "Die Wirkungen des Amyl-Nitrites." 'Archiv f. Anat. u. Phys.,' vol. 79, p. 384.

maintained in them, while their nerves remain undisturbed, the nitrite, when inhaled, still dilated the vessels of the ear to which it had no access. He therefore concluded that the dilatation results from paralysis of the vaso-motor centre.

It appeared important to study in the first instance the points at issue between these authors. The necessary experiments were performed chiefly on cats, but in control experiments rabbits were used, and yielded almost the same results.

Experiment A.—Ether administered steadily to a cat from the bottle devised for nitrite inhalation, and complete, but not profound, anæsthesia maintained throughout the experiment. The upper portion of the sternum and three upper ribs on each side having been removed, a cannula was placed in the carotid of the right side, and the right vertebral artery ligatured, whilst the carotid and the subclavian artery on the left side were placed on threads so that at any time they could be drawn forward and clamped by bull-dog forceps covered with rubber. A cannula was also placed in the cranial end of the right carotid, and artificial respiration was steadily maintained. On clamping the left subclavian and carotid arteries, a rise of blood-pressure with slowing of the pulse very rapidly ensued, probably owing to vascular constriction arising from stimulation of vaso-motor and cardio-inhibitory centres. A rapid and considerable fall of pressure ensued when the vessels were liberated.

On administering $\frac{1}{38}$ cub. centim. (0·0231 grm.; $NO_2 = 0·0091$ grm.) of pure nitrite of amyl by inhalation, the arteries being left open, a fall of pressure with subsequent pulse acceleration was recorded in ordinary course.

After a pause of 15 minutes, a record was taken of the normal pulse. The left subclavian and carotids were then clamped, so that the head was entirely cut off from the circulation. The blood-pressure first rose slightly and then remained stationary; $\frac{1}{38}$ cub. centim. of pure nitrite of amyl was now administered by inhalation; a rapid fall of pressure soon made its appearance, the lowest point being reached 35 seconds after inhalation commenced, this being almost exactly the point at which it occurred in the previous inhalation. The pressure then rose rapidly to a point considerably above the original level, but declined again slightly on the liberation of the carotid and subclavian; the decline was never to the same low level as during the administration of the nitrite when the brain was cut off from the circulation.

Experiment A.

Time.	Pulse.	Pressure.
secs.	In 1 minute.	In millims. Hg.
0	141	90
15 Ligatured subclavian	138	95
40 Ligatured carotid	111	92
50 } 75 } Inhale $\frac{1}{38}$ cub. centim. pure amyl nitrite	96	80
85	98	63
95	101	Pressure rising
105	100	
105	101	,, ,, rapidly
120	101	,, ,, ,,
135	104	113
Arteries released	..	Pressure falling rapidly
145	112	
155	120	89, lowest pressure
165	124	
170	126	Fall ceases and rise begins

NOTE.—The fall is the same on liberating the arteries if no nitrite has been previously given.

In FILEHNE'S second experiment, whilst giving nitrite by inhalation he circulated normal blood through a Rabbit's ear in which there was entire vascular isolation. In view of the variations in the diameter of the auricular vessels of the Rabbit which may occur spontaneously, and even independently of the existence of a normal connection with the central nervous system, and further, because variation might easily arise from the strength of the electrical current which FILEHNE proposed to substitute for the normal nervous impulse, results drawn from such an experiment can scarcely be regarded as conclusive.

Another method of procedure was therefore adopted by us, consisting in the rapid and temporary ligation of all arteries passing to the head, and the injection of salt solution containing a certain amount of one of the nitrites through the cranial end of the carotid artery, one of the jugular veins having been opened on the cranial side of a ligature to permit escape of blood, and so hinder the production of a possibly abnormal intravascular tension in the brain.

In all cases the nitrite to the extent of $\frac{1}{38}$ cub. centim. was dissolved in 2 cub. centims. of ·7 per cent. salt solution. It must be premised that nitrite of amyl introduced by direct injection into the general circulation, causes a fall of blood-pressure.

The invariable result was that the blood-pressure rose instead of falling, and the characteristic fall of pressure did not occur until the clamps were removed.

A single experiment selected from a large number will serve to illustrate this point.

Experiment B.—A large cat was completely anæsthetised by ether. The arteries were prepared for experiment by connecting the right carotid with the manometer, resecting the ribs and the upper part of the sternum, ligaturing the right vertebral

and placing on threads the left carotid and subclavian arteries, as well as the veins passing from the head on the same side. Artificial respiration was steadily maintained. The vagi were undivided.

Time.	Pulse.	Pressure.
secs.	In 1 minute.	In millims. Hg.
0 Before ligation or injection	108	86
18 Clamped left subclavian and veins, the jugular being opened on the cephalic side of a permanent ligature		
23	110	
28	112	
33	109	96
36 Left carotid ligatured	110	96
44 to 51 $\frac{1}{32}$ cub. centim. (= 0·0275 grm.; NO_2 = 0·0108 grm.) in 2 cub. centims. salt solution injected into carotid artery		
56	105	Rising rapidly
61	102	
66	104	
71	102	120
91	99	Slight fall
96	100	104
101	100	
Clamps removed		
106	106	Falling
111	108	,,
116	110	,,
131	115	74
141	109	84

There was no indication of any nitrite effect so long as the vessels were ligatured, although the nitrite must have passed to the medulla oblongata by vascular anastomosis, and so reached the chief vaso-motor centre. The subsequent injection of Berlin blue proved the access to the medulla in that manner.

There was a rise of pressure and slowing of the pulse from vaso-motor and vagus stimulation, as seen in the previous experiment.

The acceleration of the heart does not occur until after the ligatures are removed, the vagus inhibitory centre having been stimulated by the vascular stagnation up to this time; the stimulation of the inhibitory centre ceases on removal of the clamps, and cardiac acceleration follows in due course.

The above results, which have been repeatedly obtained, agree very closely with those of MAYER and FRIEDRICH, who found that, after all vessels passing to the brain had been ligatured for a considerable time, a fall of pressure still followed inhalation of the nitrite of amyl, and that when it had access only to the vessels of the brain no fall of pressure ensued.

Although these experiments are justified in their bearing on the question so far as it applies to the chief vaso-motor centre, *i.e.*, that situated in the medulla, it is necessary to bear in mind that additional vaso-motor centres probably exist in the

cord, and upon them the nitrites might exert an influence independent of an effect on the peripheral vessels.

No perfectly satisfactory plan of eliminating these centres is in our hands, nor is there likely to be, unless a more exact localization of their position becomes an accomplished fact. We know from the researches of GOLTZ, SCHLESINGER, VULPIAN, LISTER, and others that stimulation of a sensory nerve is capable of causing a reflex constriction of arteries after section of the cervical cord has removed the influence of centres in and above the medulla oblongata.

But it is everywhere assumed that such centres are subordinate in their function to the chief centre, and amenable to the same influences, and if we accept this, and at the same time show that the chief centre gives no evidence of paralysis when the nitrite reaches it, it would be scarcely reasonable to suppose that subordinate centres are materially affected by it. There is, however, a further positive argument for the peripheral action of the nitrites upon the vessels, derivable from the effect which may be produced by them upon the blood-pressure after division of the splanchnics. This will be dealt with in a subsequent section.

Usual Modification of Pulse and Pressure on Nitrite Inhalation.

The phases in any inhalation of nitrite as regards the effect upon the blood-pressure may for purposes of comparison be divided into three :—

1. Blood-pressure unaffected.
2. „ „ falling and remaining at lowest point.
3. „ „ rising.

The effect on the pulse does not permit of so satisfactory a division. Frequently during the first two periods the pulse may show no alteration, but in the first half of the second period retardation may often be recognized, and this may give place to an acceleration towards its close. During the third period an acceleration usually takes place, but it will be shown that the rise of pressure may occur without acceleration, and may even be attended by retardation of the pulse.

The length of time that elapses before the fall of pressure commences varies slightly according to the phase of respiration at which the administration begins, *i.e.*, whether inspiration or expiration is in progress; but if the administration commences during inspiration—and with a little care it may usually be made to do so—the variation is very slight. The first fall is usually discernible in 4·5 to 5 seconds after the commencement of inhalation, and is not preceded by any rise of pressure. The fall of pressure progresses from this point till the maximum is reached. Suppose $\frac{1}{38}$ cub. centim. of the pure α-amyl nitrite is administered for the first time to a cat—the breathing being normally active,—the fall commences in 4·5 seconds and proceeds most rapidly during the ensuing 10 seconds, in which time it amounts to from 60 to

65 per cent. of the total reduction of pressure. After this point for the next 10 seconds the fall amounting to from 20 to 30 per cent. still continues, the lowest point after a further fall being reached on an average 35 to 40 seconds after the inhalation commenced. During the time subsequent to the 20 seconds of chief reduction the fall is necessarily very slight. There is considerable uniformity in the relationship of the various phases of the fall even when the total extent differs. This will be illustrated by the contrasted experiments α and β in the appended table.

FALL of Pressure.

Experimental dose.	Total in millims.	Began.	Per cent. in 1st 10″ after fall began.	Per cent. in 2nd 10″.	Per cent. in 3rd 10″.	Per cent. after lapse of 30″.	Time of greatest fall.
α $\frac{1}{100}$ cub. centim. = 0·0088 grm.; NO_2=0·00346 grm.	25	5″	65·2	30·4	4·4	..	33
β 1st administration, $\frac{1}{42}$ cub. centim. =0·0209 grm.; NO_2=0·0823 grm.	44	5′	64	24	12	..	35
β_2 9th " " "	35	5·5′	52·3	30	17·7	..	34
γ " " "	35	5·5′	19·5	38·4	38·4	3·7	50

After repeated administrations of nitrite there is a tendency in most cases to a relative increase in the percentage of the second and third stages at the expense of the first (Exp. β and β_2 in table). Exceptionally, however, even when small doses such as the $\frac{1}{100}$ cub. centim. have been employed, no such deterioration is discernible.

In cases of repeated administration in which the extent of the fall has become reduced, the latency of the fall appears to be longer.

In such exceptional cases as that recorded (γ of the table), in which the minimal pressure is not reached for 45 to 50 seconds, the earlier part of the fall is retarded relatively to the later, and there is a tendency for the minimal pressure to be maintained for some 10 to 15 seconds, and for the succeeding rise to be slow.

The pressure is, however, in only a very small proportion of cases, long maintained at its lowest, even when the return to or towards the normal is slow. A slight upward tendency is recorded within a comparatively few seconds of the time at which the minimum was reached.

In the first administration of amyl nitrite this maintenance of minimal depression is particularly short; it is, in fact, no sooner touched than in from 5 to 8 seconds the rise commences. A more prolonged depression at the lowest point, or within two or three millims. of it, is observable when the nitrite has been given repeatedly, and this is especially the case when the administrations succeed one another rapidly. This point and the relatively long depression at or about the minimum will be referred to later on.

The rise of pressure may vary in speed even when the dose of nitrite remains equal. Amongst the circumstances which favour a rapid rise are—

1. The absence from the blood of any considerable amount of nitrite or possibly of the products of its decomposition. Hence the return is more rapid when few administrations have been made, and when a considerable interval has elapsed between the inhalations sufficient to admit of full excretion and the return of the blood to the normal.

2. From what has already been said regarding the power of vaso-motor influence to modify the nitrite effect, it follows that respiration may produce a strong effect by itself modifying the composition of the blood, and so indirectly stimulating, or to some extent weakening, the vaso-motor apparatus, central or peripheral. We do not deny that the activity of such centres may favour a reinstatement of tonus after an action upon the arterioles has produced a fall of pressure.

The respiration is itself considerably affected by nitrite of amyl, which first causes a slight slowing, succeeded by an acceleration of the breathing, amounting to from five to nine, and occasionally to twelve, respirations per minute. If, however, the administration is repeated several times without any long pause intervening, a very distinct slowing occurs. If the course of recovery of the blood-pressure is watched during these changes in respiration, it will be noticed that rapid recovery occurs, as a rule, during the acceleration of the respiration; but that after a distinct slowing has become established the rise is much more gradual. In the first condition the nitrite elimination is accelerated, and further the tonus of the arterioles is rapidly reinstated by the action of more highly oxygenated blood.

In the latter condition the respiratory centre is apparently not the only mechanism involved, as it has been noticed that the reduction in number of respirations, and the alteration in the relationship of expiration and inspiration, was very similar to the effect produced by division of both vagi, although in the latter case the breathing was somewhat deeper. Further, when this slowing effect has been produced, the vagi being intact, the respiration under the subsequent action of the nitrite after vagotomy was very much less affected than before vagotomy. There is an indication here of an action upon the terminations of the vagus in the lung, which KNOLL* has shown to be affected by many volatile substances. After frequently repeated administrations of doses of the $\frac{1}{30}$ cub. centim. of the nitrite, even if the pause between the administrations is sufficient for complete recovery of blood-pressure, the activity of the respiration centre is undoubtedly impaired. This effect occurs not only temporarily during inspiration of the nitrite of amyl, but as a more permanent condition, necessitating artificial respiration in order to prolong the life of the animal. At this time, however, when the activity of the respiratory centre has been so far reduced, it is easily demonstrated that if artificial respiration be suspended after the nitrite fall, the blood-pressure may frequently be recovered with great rapidity without any cardiac acceleration. With the much smaller doses employed in many of the experiments no such effect was produced upon respiration.

* KNOLL, 'Sitzungsbericht d. Wiener Akad., Math.-Naturw.,' vol. 68, Part 3, p. 245.

The respiration is, however, only to be considered as an indirect agency in modifying the blood-pressure. The direct causes now present themselves for consideration.

A. Acceleration of the pulse.

B. Normal return of tonus in the arterioles.

A. The acceleration of the pulse has been regarded as the chief cause of the restitution of the blood-pressure. GUTHRIE, in 1859, pointed out the occurrence of acceleration. There is no doubt that acceleration usually accompanies the return of the pressure. PICK stated that large doses cause retardation of the heart from direct action upon its muscular substance. FILEHNE and others have observed that the Frog's heart is not accelerated, but rather retarded by the nitrite. We have observed the same result with *Rana temporaria*, both from hypodermic administration to brainless animals and from exposure of the heart to very dilute nitrite vapour.

The great variation in the amount of acceleration seems to have passed almost unnoticed hitherto. The curves obtained from FICK's manometer have been measured in a very large number of experiments; and we have obtained some information on this point. The curve under inspection was divided before, during, and after the administration of the nitrite into intervals of 5 seconds, and we then measured accurately the number of beats and fractions thereof occurring in each interval. The average increase (cat) in terms of 1 minute for doses of the $\frac{1}{38}$ to $\frac{1}{42}$ cub. centim. nitrite of amyl is thirteen to twenty beats, and the chief acceleration occurs in 40 to 45 seconds after inhalation begins. The average time of occurrence of greatest reduction of pressure is 32 to 35 seconds.

Exp. B.—Full grown cat. Steady etherisation. Had received 20 minutes before one dose of pure amyl nitrite. Vagi intact.

Time.	Pulse.	Pressure.	Respiration.
secs.	Per 1 minute.	Millims.	
Before inhalation	160	139	25
0 Inhalation of $\frac{1}{50}$ cub.centim. pure nitrite of amyl = 0·0176 grm.; NO_2 = 0·0692			
5	159	139	
10	159	Falling	22·4
15	158		
20	160	..	22·4
25	161		
30	161	104	18·4
35	162		
40	165	Rising	
45	174	..	20
50	173		
55	168	..	23
60			
70	166	..	33
80			
90	164	139	

With much smaller doses than those just specified, say the $\frac{1}{100}$ cub. centim., α-amyl nitrite is still capable of causing an acceleration of pulse rate, though its extent is not so marked as after the larger dose.

The average is from 7 to 10 beats per minute. Thus, it appears that up to a certain point, acceleration is increased in proportion to the augmentation of the dose. Very large doses frequently retard the heart in all phases of their action. The time during which acceleration manifests itself may terminate abruptly at the 50th or 60th second. In either case it not unusually happens that the pulse becomes subnormal for a time. The pulse acceleration is often preceded by a distinct slowing (such an effect is observable in the experiment just quoted). This may appear 5 seconds after inhalation has commenced, and may continue 10 seconds, or occasionally for 20 seconds. The extent of this retardation is up to, but seldom beyond, the proportion of 4 beats per minute. After section of the vagi this retardation disappears, and it seems probable, therefore, that it is to be regarded as a reflex phenomenon to which the intact vagal apparatus is necessary. This effect is probably due less to an absorption of inhaled nitrite and resulting action on the vagus centre, than to a local effect on the peripheral vagi in the pulmonary tissues; it cannot be laryngeal, as the animal breathed by a tracheal cannula.

If this surmise is well founded, the vagi play the part of both afferent and efferent nerves in this reflex action.

To return to the subsequent acceleration of the heart, the following variations in the relationship of pressure and pulse have been not unfrequently observed; they may be taken as types of the more usual exceptions. An example of each will be recorded. They are taken from all stages of experiments, and, therefore, the variations in blood-pressure reaction are considerable.

(1.) An acceleration of the pulse amounting to 5–7 beats at the end of 20 seconds inhalation, lasting for 20 seconds only, and disappearing altogether before the rise of pressure has been well established.

Experiment XII., 10.—Gave $\frac{1}{48}$ cub. centim. (= 0183·0 grm.; NO_2 = 0·0072 grm.) pure α-amyl nitrite. Pressure fell from 91 to 65 millims. In 116 seconds rose to 84 but remained subnormal for 3 minutes. (Pulse accelerated 5 at end of 20 seconds, and in 40 seconds has regained the normal.)

(2.) The pressure remaining subnormal for a considerable time, followed by a slight pulse acceleration, appearing late, and disappearing before the pressure had regained the maximum.

Experiment.—Gave $\frac{1}{38}$ cub. centim. pure nitrite of amyl. Pressure fell from 96 to 70 millims. (Pulse retarded during inhalation, and only accelerated at rate of 2 beats per 1 minute 80 seconds after its termination. Thereafter slightly slowed again.)

In 1 minute recovered to 84.
,, 2 minutes ,, 87.
,, 4 ,, ,, 97.

(3.) No acceleration of the pulse occurring, but the pressure rising to its original level within 2 to 3 minutes.

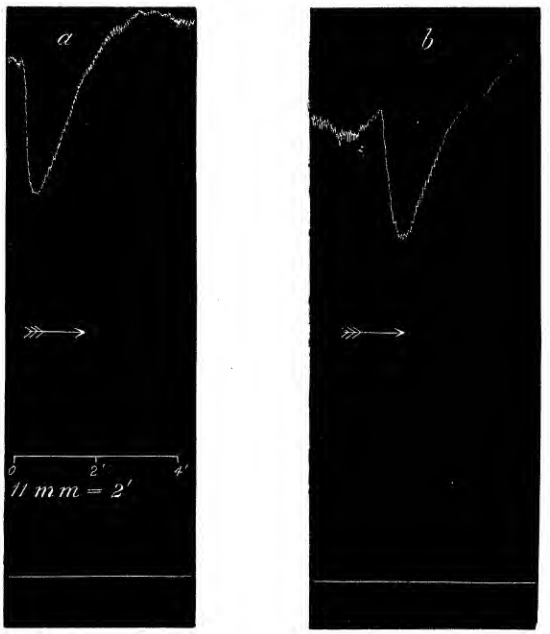
Experiment.—Gave $\frac{1}{38}$ cub. centim. pure nitrite of amyl. Pressure fell from 151 to 108. No acceleration of the pulse occurred throughout.

In 1 minute was 133 millims.
„ 2 minutes „ 150 „
„ 3 „ „ 154 „

(4.) An actual slowing of the pulse throughout (rare with nitrite of amyl for the doses examined).

The Pulse after Vagotomy.—If it were granted that the acceleration of the pulse after nitrite of amyl is owing only to a lowered tonus of the vagus centre, as has been

Tracing 1*a*. Tracing 1*b*.



Inhalation of $\frac{1}{42}$ cub. centim. α-amyl nitrite before vagotomy.

Inhalation of $\frac{1}{42}$ cub. centim. α-amyl nitrite after vagotomy.

supposed by FILEHNE and PICK, we should reasonably expect that, after both vagi had been divided, inhalation would not be followed by acceleration, and we might further anticipate that if the rise of blood pressure were only due to pulse acceleration, a very prolonged depression would necessarily follow the section. FILEHNE cut the vagi of a rabbit, and obtained—unusual in the case of such an animal—an acceleration of over 20 beats per minute. After stimulating the peripheral portion of the vagi, so as to reduce the number of heart beats to the normal, he (F.) gave nitrite by inhalation till convulsions occurred, and found that although the vessels of the ear dilated, there was no further acceleration.

Whilst admitting that the usual amount of acceleration is not attained after vagotomy, it must still be insisted that a slight acceleration is usually to be observed. This acceleration, which may not amount to more than 15 to 20 per cent. of the previous amount, usually has its maximum 30 seconds after the inhalation is begun, and lasts for a shorter time than it does when the vagi are intact.

In one experiment the regularity of the acceleration produced by amyl nitrite was greater after than before vagotomy, though in amount it fell far short of the greatest acceleration with the vagi intact. The following figures may serve to give some idea of the nitrite effect in the same animal before and after vagotomy respectively. (XII., 18.) (See tracings 1*a* and 1*b*.)*

	Before section of vagi.	After section of vagi.
	millims.	millims.
Fall of pressure . .	35	33·5
Rise to normal in. .	109	120
Pulse before . . .	162	166
Respiration. . . .	25	19

Commenced inhalation of $\frac{1}{4\frac{1}{2}}$ cub. centim. A. N. (= 0·0209 grm., NO_2 = 0·00823 grm.).

Time.	Pulse.	Respiration.	Pulse.	Respiration.
seconds.				
0				
5	159			
10	159	22·4	166	19
15	157			
20	159	22·3	166	
25	159	22·4		
35	161		171	Steady
40	169	18·4	171	,,
50	175	20	170	,,
60	168		170	,,
70	166	23	166	,,
80	168	23		
120	162			

One is therefore brought to the conclusion that small doses of pure α-amyl nitrite may accelerate the heart by directly stimulating it.

* The figures taken upon the slowly-moving cylinder from a mercurial manometer show changes in blood-pressure only. The movements of the pulse rate are taken from the rapid tracing of the FICK'S kymograph. The latter are given as figures when of sufficient importance. Where both manometers are open at the same time the form of the pulse is not accurately recorded, but its rate is reliable.

Rise of Pressure from Return of Tonus in Arterioles.

Attention has already been drawn to the fact that recovery of pressure, after small doses of pure nitrite of amyl, may occur without any direct pulse acceleration. Since no evidence of increase in the amount of blood discharged from the heart at each contraction is derivable from a study of the pulse, the return of contraction to the arterioles which had been dilated by the nitrite must be regarded as the cause of the rise. The instances (observed in cats) in which a fall of pressure was followed by a return to the normal without the occurrence of acceleration, are not those alone in which the original fall is insignificant; on the contrary this phenomenon is often observed during the earlier administrations of the nitrite in which the fall is so great as to amount to from 30 to 44 per cent. of the total pressure.

On looking over a large number of experiments (on cats) it appears that administration of from $\frac{1}{32}$ to $\frac{1}{48}$ cub. centim. of nitrite is followed, in about 27 per cent. of cases, by one of the three following conditions, (1) by a slight slowing of the pulse in 2 per cent., (2) by no alteration, (3) by an increase of one or two beats per minute. In the remaining 73 per cent. there is a marked acceleration. In cases of this exceptional nature the return of pressure is not of uniform speed, it is more rapid before the administration of nitrite has been repeated, that is to say, before a lasting impression has been produced which tends to a deterioration of the tonus of the arterioles, favouring a gradual decline in maximal blood pressure. The return of pressure was not more rapid than when (with the same animal) a distinct acceleration of the heart occurred. Companion cases of acceleration and non-acceleration, taken from the same experiments, will be placed here side by side.

	Administration.	Fall.	Recovery.	Acceleration.
	cub. centim.	millims.	′ ″	
Exp. F. . . {	$\frac{1}{50}$	26	3 3	none
	$\frac{1}{50}$	32	1 6	20 per min.
Exp. A. . . {	$\frac{1}{32}$	43	2 40	none
	$\frac{1}{32}$	44	2 33	15 per min.

If administration of the nitrite is made during the spontaneous occurrence of Traube-Hering curves, the pressure is very rapidly recovered. The increased activity of the vaso-motor centre, as evidenced by these curves, is as insufficient to prevent the fall of blood-pressure after nitrite administration, as we know splanchnic stimulation to be, but it appears to shorten the nitrite effect somewhat as in the case of splanchnic stimulation, causing a rise of pressure to the normal, with a quite unusual rapidity.

Intra-Vascular Injections of α-Amyl Nitrite.

The solutions for injections were made by introducing small measured quantities of α-amyl nitrite into the barrel of a hypodermic syringe, into which 2 or 5 cub. centims. of neutral or very slightly alkaline salt solution had been previously drawn.

The syringe was closed, shaken, and immediately fitted into the india-rubber continuation of the cannula, which had been previously introduced into the cranial end of the carotid artery, or into the central end of the saphenous vein respectively. The cannula was closed until the time for injection had arrived, when the clamp was removed and the contents of the syringe slowly expelled into the vein. The syringe was again partly filled with 2 cub. centims. saline solution and discharged into the cannula, thus driving all the nitrite solution into the circulation. The injection was made in all cases with a rapidity as nearly equal as possible. Administration of the nitrite by inhalation was made both before and after the injections for the purpose of contrast.

Intra-venous injections may be attended by a slight and transitory rise of blood pressure, amounting to from 2 to 4 millims., or this rise may be absent. A rapid fall occurs after this rise, or, in its absence, shortly after administration. A partial recovery of pressure succeeds the fall with tolerable rapidity, and this may progress steadily, or be soon arrested, the blood-pressure in the latter case returning gradually towards the normal. During the return a secondary fall is not unfrequent.

Intra-arterial injection delivered into the carotid towards the head is always attended by an initial rise, then by a more gradual fall than is shown after intra-venous injections, the point of minimal pressure being reached later, though the total fall is never so extensive.

Recovery at first rapid, usually shows a secondary fall, and then a gradual rise towards the normal.

An experiment will be quoted in which there was

α.—Administration of $\frac{1}{38}$ cub. centim. by inhalation.
β.—Administration of $\frac{1}{38}$ cub. centim. by intra-venous injection.
γ.—Administration of $\frac{1}{38}$ cub. centim. by intra-arterial injection.

The alteration of pulse as well as of pressure will be recorded in these cases.

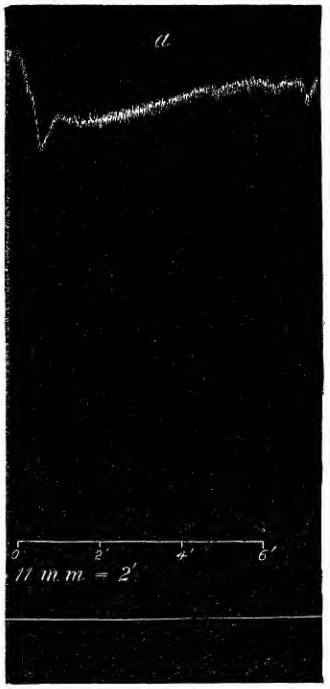
Exp.—Cat of large size. Cannulas in trachea, in the distal end of the left carotid for injection, and in the proximal end for manometer, also in saphenous vein. Steady etherisation.

A. Injection of $\frac{1}{38}$ cub. centim. of amyl nitrite dissolved in 5 cub. centims. salt solution into central end of saphenous vein. Pressure fell from 142 to 108 = 34 millims.

In 2 minutes the pressure was 113 millims.
„ 4 „ „ „ „ 118 „
„ 6 „ „ „ „ 120 „
„ 10 „ „ „ „ 148 „

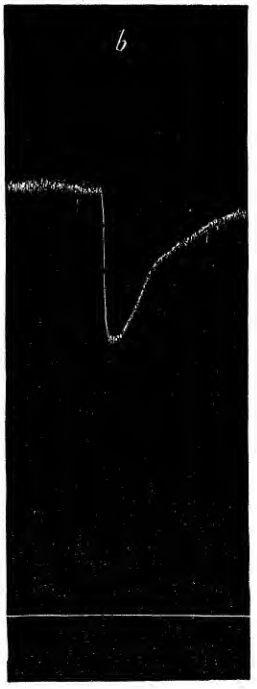
	Time.	Pulse.	Respiration.	
	secs.			
Before injection . . .	..	180	46	
During injection . . .	5	180		
	10	176	45·5	
	15	177	..	Pressure began to fall.
	20	174	45·5	
After injection . . .	5	176		
	15	177	50	
	20	..	..	Rapid fall began.
	25	177	48	
	40	185	48·5	Pressure at lowest.
	60	185	57·5	
	80	182	55	

Tracing 2*a*.



Injection by carotid artery of $\frac{1}{38}$ cub. centim. *α*-amyl nitrite.

Tracing 2*b*.



Inhalation of $\frac{1}{38}$ cub. centim. *α*-amyl nitrite.

Injection of $\frac{1}{38}$ cub. centim. of amyl nitrite in 2 cub. centims. salt solution into cranial end of *carotid*.

Original pressure 153, rose 3 millims. and then fell to 126 = 27 millims.

Fall commenced 22 seconds after injection was begun.

In 2 minutes the pressure was 133 millims.
„ 4 „ „ „ „ 139 „
„ 6 „ „ „ „ 144 „
„ 8 „ „ „ „ 145 „

	Time.	Pulse.	Respiration.	
	secs.			
Before injection . . .	..	144	40	
During injection of $\frac{1}{38}$ cub. centim. amyl nitrite.	5	145		
	10	146	38·5	
	15	145		
	20	138	36	Injection finished.
Tracing 2a.	35	143	38·5	
	40	..	..	Rapid fall of pressure began.
	45	146	40	
	55	146	39·5	
	60	145	39·5	
	90	145	40	
	100	141	38·5	
	120	137	40	

After two more injections had been made, a marked deterioration of the blood-pressure was produced. At this time (40 minutes after the injection just described) an inhalation was given of $\frac{1}{38}$ cub. centim. of pure nitrite of amyl, with the following results.

Blood-pressure fell from 114 to 75 millims. Tracing 2b.

Fall commenced in 55 seconds.
In 2 minutes pressure was 101·5.
„ 3 minutes 50 seconds pressure was 110.

	Time.	Pulse.	Respiration.
	secs.		
Before inhalation	..	141	40
During inhalation lasting	20	140	41
After inhalation	20	146	44
	35	154	46
	55	157	45
	70	150	42
	85	148	40
	95	144	38

It has been found that this relationship of the effects produced by α-amyl nitrite are very constant according to the mode of administration.

The greatest total reduction of pressure is produced by inhalation ; but this is the least prolonged in its action. The minimal pressure is recorded sooner after inhala-

tion. The fall of pressure after intra-venous injection is greater than that following intra-arterial injection. After the latter the initial rise is always more marked than after the former.

Pulse acceleration is greater after inhalation than after intra-venous injection, and is least in intra-arterial injection. This relationship will be compared with that obtained on injection of iso-butyl nitrite, primary propyl nitrite, and ethyl nitrite respectively. It will be shown that the series which may be formed, according to the activity of the various nitrites in reducing blood-pressure, is not identical for administration by inhalation and intra-venous injection respectively.

Intra-venous injection of $\frac{1}{100}$ cub. centim. of α-amyl nitrite produces a marked reduction of pressure with pulse acceleration.

IV.—The Action of other Paraffinic Nitrites contrasted with that of Amyl Nitrite.

The number of experiments which have been requisite to afford a contrast of the following nitrites one with another has necessarily been large; for it was evident from the first that the only reliable means of comparison was to be obtained by administering certain of them to the same animal under conditions as nearly similar as possible. Several repetitions of each experiment were necessary for confirmation.

We have already mentioned some of the directions in which special precautions were taken, such as:—

(1.) The administration of equal quantities by volume of the nitrites, as estimated by very delicate measurements.

(2.) The steady and uniform administration of ether.

(3.) The maintenance of the temperature of the animal by keeping it in a warm box.

It has been shown in what ways the ordinary effect of pure α-nitrite of amyl may undergo modifications, and these variations have been somewhat accentuated to show the difficulties which must attend the contrast of a number of bodies which may vary so largely in their action on individuals.

After limiting the series which had been accumulated for the purpose of contrast by rejecting experiments in which the results were in any way doubtful, and after filling up the gaps by subsequent experiment, where it seemed necessary, it became possible to establish certain distinctions between the action of the bodies examined.

The relative effect produced by the various nitrites administered to the same animal, under as nearly similar conditions as possible, has been the guide in arranging them in order of activity. Whilst this order is deduced from a very large number of experiments it will only be possible to give a few examples of the results. Within certain limits animals differ in the degree of reaction they manifest towards the nitrites so that a large dose to one will be productive of no greater result than a

medium dose to another. The comparison of the action in various experiments must be conducted cautiously, at least two compounds being employed in each. It will be shown that, whilst the total effect of any one nitrite may vary in different experiments, its variation runs parallel with those of other nitrites. Thus amyl nitrite may produce a greater fall of pressure in Experiment B than in A; the same result will be obtained with iso-butyl nitrite, only the effect in both experiments is proportionately greater than that of the amyl compound.

Pure α-amyl nitrite has been already somewhat fully dealt with, so that reference can be made to its action for the purpose of contrasting with it other nearly related bodies, which contain a certain amount of β-nitrite.

The bodies were the following:—

		Per cent.	Marked.
(1.)	Amyl nitrite containing α-nitrite	95	I.
	,, ,, ,, β- ,,	5	
(2.)	,, ,, ,, α- ,,	88·6	II.
	,, ,, ,, β- ,,	11·4	
(3.)	,, ,, ,, α- ,,	84·6	III.
	,, ,, ,, β- ,,	15·4	

These bodies were closely contrasted with the pure α-amyl nitrite, with one another, and also with the other members of the series of nitrites in which bases other than amyl were present.

They show amongst themselves only small variations in their activity upon the blood-pressure and pulse of animals examined under similar circumstances.

From nine experiments which dealt wholly, or in part, with the contrasted action of these bodies, the following facts have become clear:—

(1.) That the blood-pressure is reduced to a somewhat greater extent by the pure α-nitrite than by the other three. This difference in reduction is at most but a slight one, the proportionate increase from pure α-amyl nitrite being only about 3 per cent. above the next in activity of the three mixed nitrites, and not over 6 per cent. above the weakest.

These three bodies appear to fall into the following series when their pressure-reducing action is contrasted:—(1.) Most active (2.) Intermediate, between 1 and 3. (3.) Least active.

On consulting the table furnishing the composition of these bodies, it becomes evident that, at one end of the scale in this series, the pure α-amyl nitrite must be placed as the most active member, whilst at the other end is the mixed body containing the largest proportion of β-nitrite. The other two mixed nitrites take an intermediate position.

It has been said already that the variation in the activity of these bodies upon blood-pressure is really very small, and it may be stated here that though the repetition

of experiments made it evident that a difference did exist between them, such as has now been indicated, we were at first inclined to believe their action identical.

The action of the mixed amyl nitrite group may be summarised by stating that the fall of pressure, the duration of depression, the speed and manner of its recovery, are closely similar with the exception of the slight variation already referred to.

The fall of pressure induced by their action is not, however, the only criterion by which we can contrast nitrite effects. The influence on the pulse is another in which a variation may be sought. It is not evident that any wider distinction exists between the various amyl nitrites in this respect. They, as a group, cause a relatively considerable acceleration in the heart-beats, and their action in this respect contrasts with the group in which alkyls other than amyl are present.

It has been pointed out that, according to the mode of administration, whether by inhalation or intra-vascular injection, &c., the action of α-amyl nitrite varies. Only one other member of the mixtures of amyl nitrites was tested by injection, but it was found that the two compounds were identical in their manifestations, with the exception of a slightly greater effect of α-amyl nitrite on the blood-pressure.

Tertiary Amyl Nitrite.

Contrasted with α-amyl nitrite this body proved itself more active in reducing the blood-pressure, whether administered by inhalation or injection. Especially by the latter method its greater activity is observable in the relatively greater extent of the fall of pressure and its more gradual recovery. It is worthy of note that, while after inhalation of the tertiary amyl nitrite the pulse is usually accelerated at least two beats above the effect caused by the primary compound, the result after injection was the opposite, and this may have contributed to the difference observed in the speed of recovery of blood-pressure.

In a sub-series of ten of the nitrites which were administered at the same period (February and March, 1890), and the results produced by which are strictly comparable, it was found that the primary and tertiary amyl nitrites were the two most active bodies in causing acceleration, though they came only midway as regards their power of reducing blood-pressure.

The prolonged effect of the tertiary compound on injection is striking.

The average reduction of pressure after $\frac{1}{100}$ cub. centim., given either by inhalation or injection, appears to be from 26 millims. to 31 millims. The recovery of pressure is slower than in the case of the primary compound.

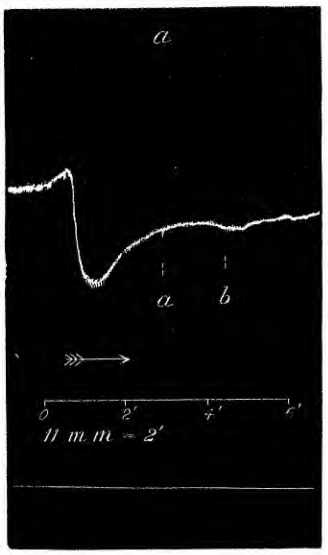
Tertiary amyl nitrite does not actively affect the respiration in the dose of $\frac{1}{50}$ cub. centim. (= 0·0178 grm. ; NO_2 ·007 grm.) although it causes a slight slowing at first, occasionally followed by a faint acceleration.

The following figures will give an idea of the extent to which retardation in rise of blood-pressure may follow tertiary amyl nitrite inhalation.

Inhalation of Tertiary Amyl Nitrite.

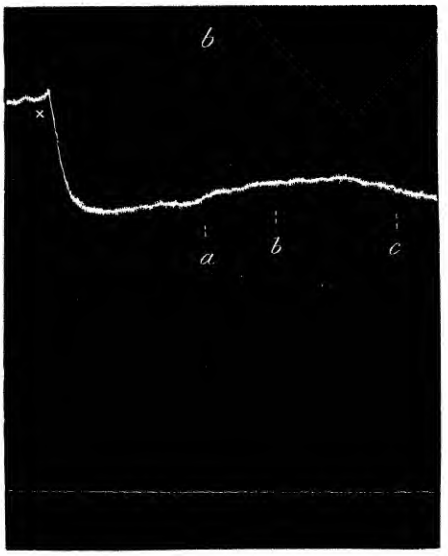
(25.3.90.) Cat of 5 lbs. Cannula in femoral vein. Breathing normally by the tracheal tube. Ordinary arrangement of apparatus. After tertiary amyl nitrite had been thrice administered by inhalation, $\frac{1}{100}$ cub. centim. (= 0·0089 grm.; NO_2 = 0·0035 grm.) was given. Tracing 3*a*.

Tracing 3*a*.



Inhalation of $\frac{1}{100}$ cub. centim. tertiary amyl nitrite.

Tracing 3*b*.



Injection by femoral vein of $\frac{1}{100}$ cub. centim. tertiary amyl nitrite.

The blood-pressure which at the commencement was 83 millims. fell in 40 seconds to 55 millims.

In 2 minutes the pressure was 69 millims.
„ 4 „ „ „ 70 „
„ 6 „ „ „ 74 „

The heart was accelerated at the rate of 14 beats per minute for 50 seconds, and the respiration 1 per minute.

Same animal. Injection of $\frac{1}{100}$ cub. centim. into circulation through femoral vein. Tracing 3*b*.

	Time.	Blood-pressure.	Pulse.	Respiration.
	secs.	millims.		
Before injection	0	107	146	43
$\frac{1}{100}$ cub. centim. tertiary amyl nitrite in 5 cub. centims. salt solution injected into femoral vein	5	..	143	
	15	..	144	42
	25	..	144	
	35	..	144	
	45	..	146	40
	55	..	149	
	65	76	155	41
	85	..	155	
	95	..	155	
	210	82	153	
	340	..	120	42
	490	..	118	43
	680	83		

The *butyl compounds* examined were the following :—

Normal (primary) butyl nitrite.
Iso-butyl nitrite.
Secondary butyl nitrite.
Tertiary ,,

Primary Butyl Nitrite.

Primary butyl nitrite will be first considered in this group ; it stands physiologically somewhat removed from the other members.

It separates itself from iso-butyl nitrite by its comparatively feeble action, whether administered by inhalation or intra-vascular injection. Inhalations of doses of $\frac{1}{100}$ cub. centim. (= 0·0088 grm. ; NO_2 = 0·00393 grm.) of butyl nitrite are followed by a prompt fall of pressure which varies in extent from 15 to 23 millims. The average fall observed in a large number of inhalations is 19 millims.

In average cases at the end of five minutes after the administration of such a dose the pressure is subnormal to the extent of 4 millims.

The speed of recovery of pressure cannot, however, be predicted with precision from the extent of the fall. A great fall may be succeeded by a prompt return to the normal within as short a time as 160 seconds, and on the other hand an insignificant fall may be maintained for a considerable time. In the former case the vaso-motor apparatus is active, and the vessels rapidly regain their tone ; in the latter an opposite condition obtains ; it is most commonly associated with the prevalence of a low pressure.

In small doses nitrite of butyl does not markedly accelerate the pulse. Taking the results of six inhalations from three distinct experiments, acceleration appeared in half the number, in two there was no alteration, and in one a slight retardation

throughout. The average result of a large number of experiments in which $\frac{1}{100}$ cub. centim. was administered was found to be an acceleration of from four to five heart beats per minute. Such acceleration as may be produced is of rapid occurrence, and is frequently observed in 30 seconds after the commencement of inhalation. Respiration is retarded to the extent of four or five per minute after inhalations of $\frac{1}{100}$ cub. centim. butyl nitrite.

The contrast of butyl nitrite with amyl nitrite when given by inhalation shows the latter to be slightly more powerful in reducing pressure, somewhat more lasting in its effect, and more usually accompanied by acceleration. It has less effect upon respiration than the butyl compound.

Butyl nitrite when given by injection causes a more marked fall of pressure than when given by inhalation. When it is given by the former method the average fall is 23 millims., or about 17 per cent. more. In that case the fall is succeeded by even less acceleration of the pulse than when the nitrite is given by inhalation, from one to three beats per minute being the usual increase. The rise of pressure is slightly less rapid after the injection. Five minutes after the commencement there is still an average deficiency of from 5 to 8 millims.

(20.2.90.) Cat of 5 lbs. Steadily etherised. Administration of $\frac{1}{100}$ cub. centim. butyl nitrite in 5 cub. centims. salt solution by injection into femoral vein. The blood-pressure fell 22 millims. (124–102), and in five minutes was 115 millims. Tracing 4*a*, 4*b* (slow and quick drums).

	Time.	Pulse.
	secs.	
Before inhalation . .	..	133
During injection . .	0	130
	5	130
	15	132
	25	133
	40	133
	50	133
	70	132
	90	134
	110	132
	150	132
	240	138

Iso-butyl Nitrite.

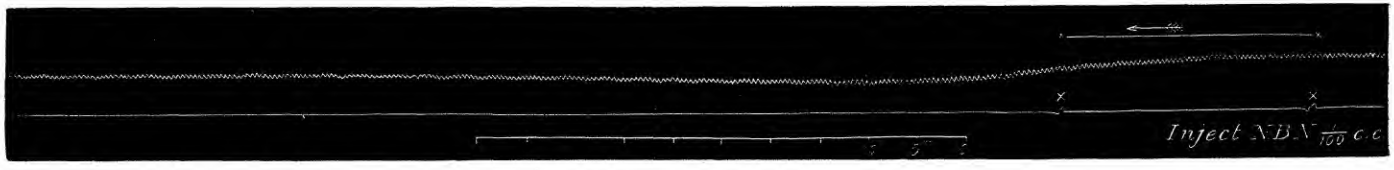
This is one of the most active bodies examined in the whole series as regards the reduction of blood-pressure. Not only is this reduction of great extent, but it is produced with rapidity, so that the point of minimal pressure is soon reached.

As in all the nitrites examined, the earliest administrations of the drug produce

Tracing 4*a*.

Injection by femoral vein of $\frac{1}{100}$ cub. centim. butyl nitrite. For changes in pulse see fig. 4[1].

Tracing 4*b*.



Injection by femoral vein of $\frac{1}{100}$ cub. centim. butyl nitrite in 5 cub. centims. salt solution. Reduced one-half. The upper tracing taken with FICK's kymograph, shows pulse and pressure; the lower, from a MAREY's tambour, shows respiration, the point as in all experiments moving upwards on inspiration. For changes in pressure see record by mercurial manometer (4) on slow cylinder.

the above effects in the most marked degree. As the number of administrations is multiplied, a general deterioration in the blood-pressure becomes apparent, and the active nitrite fall is reduced in extent, though it still bears about the original relationship to the lower pressure which the greater fall did to the higher.

Under the progressive action of the drug, however, the return of pressure to or towards the normal is distinctly retarded, so that the time during which the pressure remains subnormal shows an increase with successive administrations.

The pulse rate is usually affected by inhalations of iso-butyl nitrite, but the modification it undergoes is not parallel with that which follows the action of pure α-amyl and tertiary amyl nitrites. In the earlier stages of its action—*i.e.*, subsequent to the first 15 seconds of administration of $\frac{1}{40}$ cub. centim. (= 0·0348 grm.; NO_2 = 0·0152 grm.)—an acceleration having the value of 4 to 5 beats per minute is witnessed, and this gives place to a further slight acceleration in the succeeding 20 or 25 seconds.

If the action of iso-butyl nitrite in this respect is contrasted with members of the amyl group, it becomes evident that the total acceleration produced by the former is by no means so marked as that produced by the latter, therefore the fall of pressure is not the only cause of acceleration.

The return of pressure to the normal is not dependent alone upon the pulse acceleration, as the pressure after iso-nitrite of butyl usually recovered more rapidly than after amyl nitrite, although the fall of pressure is much greater after the former, while the pulse acceleration is less.

From the rapid fall of pressure following the administration of iso-butyl nitrite, it is evident that a very prompt and complete vascular dilatation occurs.

This effect is not, however, of prolonged duration, the blood-pressure tends to rise rapidly, and often accompanied with a slight acceleration of the pulse; the returning tone of the vessels evidently playing an active part in this recovery.

The following experiment will serve to illustrate these points:—

Cat of 7 lbs. Steadily etherised from tracheal cannula. Vagi intact. Breathing natural. Tracings 5*a* and 5*b* (slow and quick cylinders).

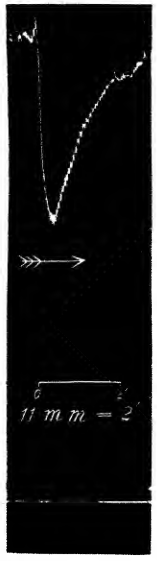
Administered iso-butyl nitrite by inhalation.

$\frac{1}{50}$ cub. centim. (= 0·0174 grm.; NO_2 = 0·0038 grm.).

Pressure rose 4 millims., and then fell.

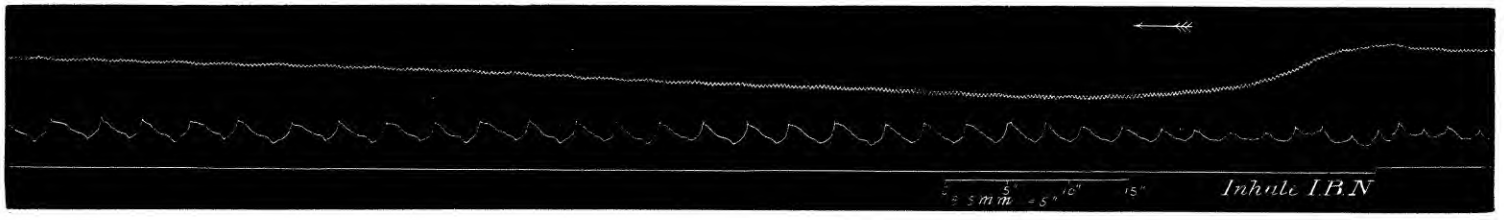
54 millims. (128–7 4 millims.). In 2 minutes it rose to 111; in 350 seconds to 117 millims.

Tracing 5*a*.



Inhalation of $\frac{1}{50}$ cub. centim. iso-butyl nitrite. (For pulse and respiratory tracings, see tracing 5*b*.)

Tracing 5*b*.



Inhalation of $\frac{1}{50}$ cub. centim. iso-butyl nitrite. Reduced one half. The upper line shows pulse and pressure, the second respiration, the lowest the signal marking time of administration. For pressure changes, see tracing 5*a*.

	Time.	Pulse.	Respiration.
	secs.		
	0	204	27
	5	204	
Admitted I.B.N.	10	205	27
	15	204	
	20	206	21·5
	25	204	
	30	206	20
	40	206	18·5
	50	200	13·5
	60	196	18
	70	196	17·5
	80	192	17
	90	192	16
	100	200	17
	105	204	17·5
	110	208	
	115	204	17
	125	..	17
	135	206	17
	180	..	22
	210	204	23

Before the administration the heart was accelerated, and the breathing was also rapid. The pulse showed a slight tendency to accelerate after the nitrite; the respiration on the other hand became slower, and remained subnormal for several minutes. Of course when the initial pulse rate is high, so large an acceleration is not to be expected as in cases when the initial rate is low.

Experiment.—Cat of $6\frac{1}{4}$ lbs. Usual preparation. Steady etherisation. Administration of $\frac{1}{48}$ cub. centim. (= 0·0182 grm.; NO_2 = 0·0079 grm.). The fall of pressure commenced 4 seconds after administration.

In 25 seconds it fell from 135 to 80 millims.
„ 90 „ pressure rose to 107 „
„ 110 „ „ 129 „

	Time.	Pulse.
	secs.	
Before nitrite	..	185
During „	15	182·5
	25	186
	30	186
	35	188
	45	190
	60	192
	75	192
	95	188
	115	180

With the result of this inhalation we can contrast one made with the mixed α and β-amyl nitrite (1) $\frac{1}{48}$ cub. centim. (= 0·018392 grm.; NO_2 = 0·00972 grm.).

Here the pressure fell from 121 to 77, or through 44 millims. The lowest pressure was reached in 30 seconds.

In 1 minute it had risen to 96.
„ 2 minutes „ „ 113.
„ 2 „ 54 seconds it had risen to the normal.

Greatest acceleration of the pulse amounted to 24 beats per minute.

Small doses.—Administration of such small doses as $\frac{1}{80}$ to $\frac{1}{100}$ cub. centim. of isobutyl nitrite by inhalation produces a marked fall in pressure, placing it much beyond the action of α-amyl nitrite and primary butyl nitrite.

The average reduction of pressure it induces in doses of $\frac{1}{100}$ cub. centim. is 45 to 50 millims., whilst the return of pressure is accompanied by an acceleration of the pulse rate averaging 4 to 7 per minute.

As to the duration of its action this appears to be somewhat shorter than after amyl nitrite, as the pressure is about normal in five minutes after the commencement of inhalation, whereas after amyl it is still subnormal at this time.

The bulk of the recovery, that is to say, from 70 to 75 per cent. of it, is in fact usually made in early inhalations, just within two minutes of the time when inhalation was commenced; the ascent after this shows a relative retardation which accounts for the total time occupied.

It is, however, no uncommon occurrence by a greater acceleration during the last stage for the pressure to regain the normal after a fall of 45 to 50 millims. in 3 minutes 30 seconds.

As with the larger dose so with the $\frac{1}{100}$ cub. centim. (= 0·0087 grm.; NO_2 = 0·0038 grm.), administered for the first few times, the breathing is greatly retarded, and even arrested for 20 or 30 seconds, but subsequently this tendency becomes less observable.

This effect, as well as the accelerated respiration which occasionally succeeds it, modifies the course of the blood-pressure.

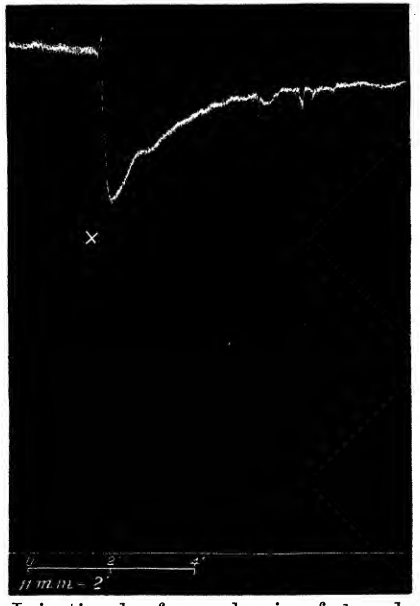
Experiment G.—Tracing 6*a* and 6*b* (quick and slow cylinders). Cat of $6\frac{1}{2}$ lbs. Cannula in carotid. Usual arrangement of apparatus. Normal amyl nitrite had already been given, but had not affected respiration.

The blood-pressure fell 50 millims., and became normal again in 3 minutes 22 seconds.

Tracing 6*a*.

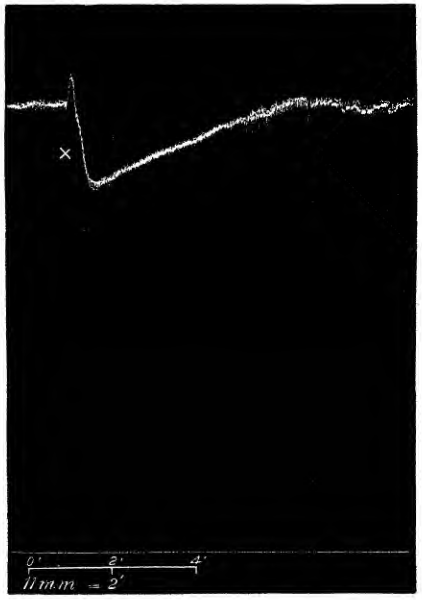
Inhalation of $\frac{1}{80}$ cub. centim. iso-butyl nitrite. The letters correspond with those in tracing 6*b* recorded on rapid cylinder.

Tracing 7*a*.



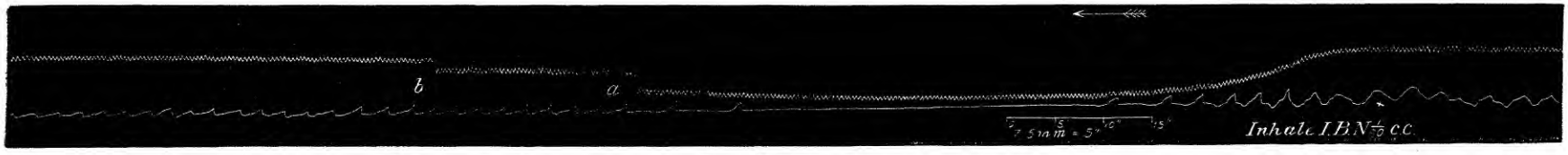
Injection by femoral vein of $\frac{1}{38}$ cub. centim. iso-butyl nitrite.

Tracing 7*b*.



Injection by carotid artery of $\frac{1}{38}$ cub. centim. iso-butyl nitrite.

Tracing 6*b*.



Inhalation of $\frac{1}{80}$ cub. centim. iso-butyl nitrite. Reduced one-half. The letters correspond with those in the corresponding slow record, tracing 6*a*. The upper line shows pulse; the lower, respiration. A star indicates the time of commencing administration.

	Time.	Pulse.	Respiration.
	secs.		
Before nitrite	..	148	22
Inhaled $\frac{1}{80}$ cub. centim. iso-butyl nitrite	5	151	
	10	156	21
	15	159	
	20	162	21
	25	161	1
	30	158	
	35	156	
	40	..	Stopped.
	45	154	
	60	152	
	65	..	Recommenced.
	136	153	25
	210	156	25

Intra-vascular Administration of Iso-Butyl Nitrite.—The same small doses were used in these experiments which had been employed in inhalation.

The nitrite was discharged from the measuring pipette into salt solution previously introduced into the inverted barrel of a hypodermic syringe, which, after being well shaken, was fitted into the cannula.

The result differs according as the injection is made into the cranial end of the carotid artery, or into the central end of the saphenous vein.

27.5.90.—*Experiment.* After the *intra-arterial* injection in the experiment quoted, a comparatively slow fall was preceded by a distinct rise in pressure, the reduction of pressure was moderate (30 millims.), and its recovery fairly rapid (294 seconds). After the intra-venous injection, a much more abrupt and extensive fall of 45 millims. was preceded by only a slight rise of 5 millims., and the recovery of pressure, though at first more rapid, was ultimately slower; after 6 minutes it was still subnormal. Tracing 7*a*.

The period at which the fall begins likewise varied in the two cases.

After the venous injection the pressure fell below the initial pressure in 10 seconds, but after the carotid injection it fell in 16 seconds. In the former, the lowest pressure is reached in 37 seconds; while in the latter, it is reached in 52 seconds.

Changes in the pulse were as follows :—

	Time.	Pulse.
	secs.	
Before injection	..	164
During 20 seconds injection of $\frac{1}{38}$ cub. centim. (= 0·0229 grm.; NO_2 = 0·08 grm.) iso-butyl nitrite by saphenous vein	..	164
After injection finished	5	165
	10	160
	15	158
After injection	20	157
	25	156
	30	155
	35	157
	40	158
	45	159
	55	159
	65	160
	85	160
	105	156
	125	157
	145	160
	185	167

Injection into carotid artery of $\frac{1}{38}$ cub. centim. 25 minutes after the injection just recorded. Tracing 7*b*.

	Time.	Pulse.
	secs.	
Pulse before	..	156
During injection into carotid artery (30 seconds)	..	156
After	5	157
	10	150
	15	146
	20	145
	25	145
	30	145
	35	149
	40	151
	50	151
	75	152
	85	156
	100	156
	140	151
	175	156
	210	153

The absence of any acceleration during the first 3 minutes is marked, as is the presence of a positive retardation amounting to 9 beats per minute in the intra-saphenous injections, and to 11 beats in the intra-carotid.

Injection of small doses of Iso-Butyl Nitrite.—A dose of $\frac{1}{100}$ cub. centim. is more

active in causing a fall of blood-pressure when administered by inhalation than by intravenous injection. The average fall it produces in the latter case is 34 millims. and the return of pressure to the normal is slightly later than in the case of inhalation. Under these conditions the pulse acceleration, if it occurs at all, amounts to not more than 4 per cent.

Localisation of action of Iso-Butyl Nitrite.—The series of experiments employed in determining the mode of action of α-amyl nitrite was repeated in the case of iso-butyl nitrite (p. 520, *et seq.*).

The general results obtained were similar, indicating a peripheral rather than a central effect. The tendency to an elevation of blood-pressure when the injection of the compound in solution was made toward the head, was a marked result, as was the fall of blood-pressure when administered by inhalation after all the vessels passing to the head had been temporarily ligatured.

Action of Iso-Butyl Nitrite on Respiration.—A marked retardation of respiration or even arrest in expiration is produced by this body. This result is well illustrated in tracing 6a (fast drum) in this tracing the retardation of respiration causes a check in the recovery of pressure; a subsequent rapid recovery occurring after the respiration is re-established. The serious and lasting interference with respiration which methyl nitrite occasions is not produced by the nitrite under consideration.

Secondary Butyl Nitrite.

This compound shares to a large extent the powerful properties of iso-butyl nitrite.

It causes a rapid and considerable fall in blood-pressure, followed by a recovery towards the normal which is usually rapid in its commencement, but tends to become slower as it approximates to the original level.

The fall is equal to, or slightly more considerable than, that of iso-butyl nitrite, and the recovery appears to be slower. An examination of the pulse rate shows a decided retardation during inhalation succeeded by a somewhat slowly developing acceleration. This acceleration is by no means an extensive one, and in this respect the drug appears to stand near the iso-butyl nitrite, and to differ from the amyl compound.

When so small a dose as the $\frac{1}{100}$ cub. centim. of secondary butyl nitrite is inhaled or injected, it produces a marked reduction in the blood-pressure.

The average fall after inhalation is 43 to 52 millims., and the recovery of pressure occurs slightly later than after either iso-butyl nitrite or tertiary butyl nitrite. The acceleration of the pulse is not extensive (frequently 5 to 7 per minute), as in the case of butyl nitrite. It may be absent altogether till late in the course of administration as illustrated by tracing 8. On respiration it has a powerful effect, causing a very marked retardation, frequently with a tendency to pause in inspiration.

The following experiment may illustrate the action of this body, though the effect is somewhat subnormal.

31.5.90.—*Experiment.* Cat (large). Steadily etherized by special apparatus. Vagi intact and breathing natural. Tracing 8.

1. Administration of $\frac{1}{100}$ cub. centim. (= 0·0087 grm.; NO_2 = 0·0038 grm.) of *secondary butyl nitrite.* Fall commenced in 4 seconds. Blood-pressure fell 43 millims. (115 to 72) its lowest point reached 32 seconds after inhalation commenced.

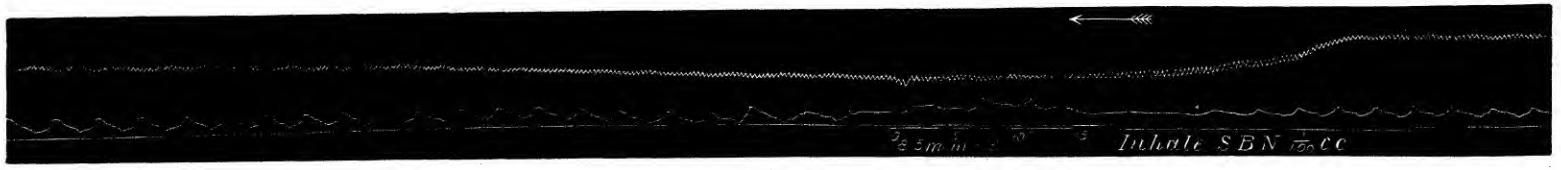
In 2 minutes blood-pressure rose to 100 millims.
„ 7 „ „ „ „ 112 „

	Time.	Pulse.	Respiration.
	secs.		
Before inhalation . . .	0	176	19·5
Inhalation commenced	5	174	
	10	174	19·5
	15	173	
	20	172	Pause in position between expiration and inspiration
	30	168	
	40	172	
	50	174	12
	70	174	15
	80	174	17
	90	175	18
	100	181	18
	110	181	20
	120	184	19·5
	135	182	17·5
	150	180	17·5
	160	175	15
	230	170	15

Secondary butyl nitrite when injected ranks as one of the most active of the nitrites, but when thus administered its effect is less than after inhalation by some 5 to 6 millims. in the fall of pressure.

If the average fall after inhalation is 43 to 53 millims., after injection it is 40 to 45; while after injection, the return is comparatively rapid (average pressure is — 6 millims. in 5 minutes) in spite of the fact that acceleration is usually no more than 1 to 3 per minute. The fall after injection is slightly greater than after an equal dose of iso-butyl nitrite.

Tracing 8.



Inhalation of $\frac{1}{100}$ cub. centim. secondary butyl nitrite. Reduced one-half. The upper line shows pulse and pressure; the second, the respiration; the lowest, the signal giving time of administration.

Tracing 9.

Injection by femoral vein $\frac{1}{100}$ cub. centim. secondary butyl nitrite.

SECONDARY butyl nitrite.

31.5.90.—The pressure fell 41 millims. In 5 minutes was 7 millims. Tracing 9.

	Time.	Pulse.
	secs.	
Before	..	133
Injection of $\frac{1}{100}$ cub. centim. secondary butyl nitrite by femoral vein	0	
	10	133
	15	128
	20	127
	30	134
	40	133
	50	132
	80	132
	100	133
	160	127

Tertiary Butyl Nitrite.

The compound now to be considered is one of the most active in the series in its effect upon blood-pressure. It acts like iso-butyl nitrite in reducing the pressure with great rapidity and power, doses so small as the $\frac{1}{32}$ to $\frac{1}{40}$ cub. centim.* usually causing a fall amounting to 40 per cent. of the entire blood-pressure, and even so small a dose as the $\frac{1}{100}$ cub. centim. produces a large reduction.

After the greater part of the fall has occurred rapidly the point of minimal pressure is somewhat gradually reached, and the rise then commences. Even in the earliest stage this rise is more gradual than that after iso-butyl nitrite; and as the phase develops, the relative retardation becomes even more apparent, the pressure remaining subnormal much longer. This effect is not attributable to cumulative action from frequent repetition of the nitrite dose, for it occurs in instances of first inhalations; nor does it take place merely as a part of a general peculiarity in individual reaction to the nitrites, as the iso-butyl nitrite or one of the amyl nitrites administered after it will be succeeded by a relatively rapid recovery to the original pressure. The early part of the action is clearly that of the butyl compounds; the latter part differs from them in the greater duration of the effect.

The earlier part of recovery of pressure is usually decidedly slower after this nitrite than after those just mentioned.

The pulse variation runs parallel at first with that of the iso-butyl nitrite; slight retardation is not unusual during inhalation, and some degree of acceleration may be

* During one experiment the effect produced was very remarkable. The $\frac{1}{30}$ cub. centim. reduced the pressure on administration 106 millims.; a second inhalation reduced it from 150 to 20, respiration being completely paralysed, but recovery occurred after artificial respiration. Subsequently a fall of 70 millims. resulted from the administration of $\frac{1}{100}$ cub. centim. only.

noticed in from 20 to 30 seconds; this acceleration is usually 10 to 14 beats per minute (for the $\frac{1}{30}$ to $\frac{1}{40}$ cub. centim.), but after the lapse of 80 to 100 seconds a more marked acceleration makes its appearance, and may continue for several minutes.

The following figures are taken from an experiment in which the action of the butyl compounds was closely contrasted. Tracing 10*a* and 10*b*, quick and slow drums.

Cat of $4\frac{1}{2}$ pounds; receiving ether steadily; breathing naturally. Administered $\frac{1}{80}$ cub. centim. (= 0·0107 grm.; NO_2 = 0·0046 grm.) tertiary butyl nitrite.

Fall commenced in 5 seconds.

Pressure fell 55 millims. in 55 seconds (118–63).

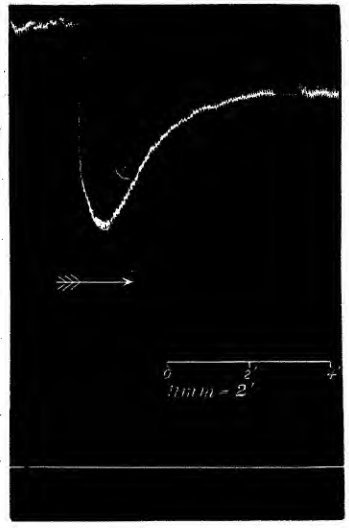
In 2 minutes rose to 90 millims.
,, 4 ,, ,, ,, 98 ,,
,, 8 ,, ,, ,, 103 ,,

	Time.	Pulse.	Respiration.
	secs.		
Before inhalation . .	0	174	27
Commenced inhalation of tertiary butyl nitrite $\frac{1}{80}$ cub. centim.	5	168	
	10	172	Two respirations occur, passing gradually into partial inspiration at end of 20 seconds and of 55 seconds
	15	176	
	20	178	
	25	172	
	30	172	
	40	174	20
	50	180	20·5
	60	180	
	70	182	20
	80	186	20
	90	183	19·5
	100	180	19·5
	110	186	17
	130	184	15·5
	160	186	16
	200	186	16
	230	192	18·5
	266	198	19·5

The action which is produced in this experiment upon respiration is very marked; a prolonged pause is only broken by one faint expiratory effort during 35 seconds when respiration recommences.

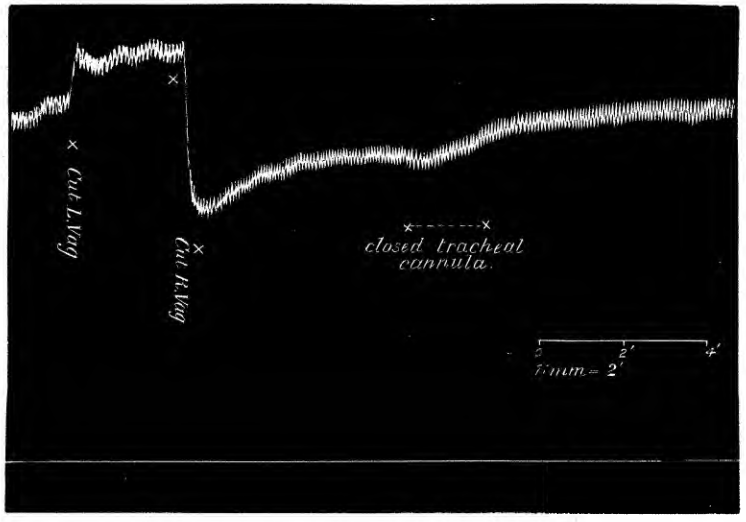
Section of Vagi. Tracing 11.—Section of vagi immediately after greatest reduction of pressure. After obtaining a reduction of the blood-pressure, very similar to that just described, $\frac{1}{100}$ cub. centim. tertiary butyl nitrite was administered, artificial respiration being carried on. The pulse, originally 144, fell to 141 during inhalation,

Tracing 10*a*.



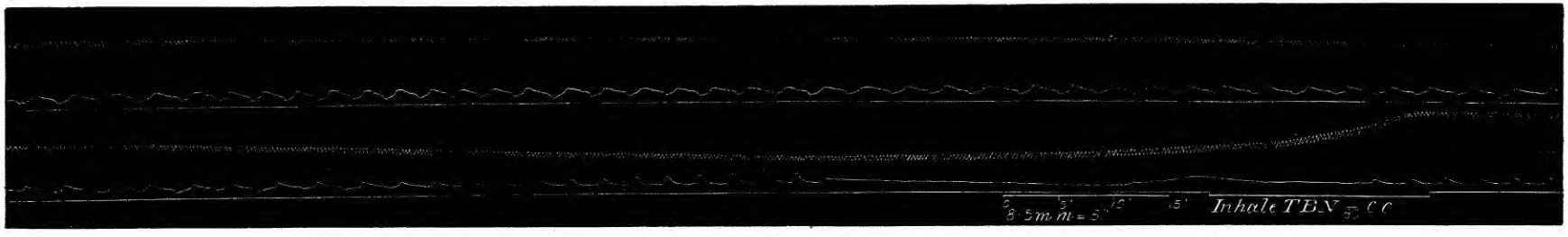
Inhalation of $\frac{1}{80}$ cub. centim. tertiary butyl nitrite. (For pulse and respiration, see quick tracing, 10*b*.)

Tracing 11.



Inhalation of $\frac{1}{100}$ cub. centim. tertiary butyl nitrite. Section of both vagi is made, that of the second being at the point of lowest pressure. The tracheal cannula is subsequently closed for 50 seconds.

Tracing 10*b*.



Inhalation of $\frac{1}{80}$ cub. centim. tertiary butyl nitrite. Reduced one-half. The upper series is continuous with the lower. The top line in each series shows pulse and pressure; the second, respiration; the lowest, the signal record of administration. See also pressure tracing (10*a*), taken on slow drum.

and then rose to the original number. The right vagus was then divided, the left having been already cut, but no acceleration in pulse-rate ensued, the number varying during the ensuing 5 minutes from 137 to 144. The pressure showed but little tendency to rise, though a considerable reduction in the calibre of the tracheal cannula produced some effect upon it.

The pressure varied as follows :—

Pressure 109 millims. fell to 67 millims. in 45 seconds.
30 seconds after commencing inhalation divided vagi.
2 minutes pressure 76 millims.
4 „ „ 81·5 millims.
6 „ „ 81 millims., partly closed tracheal cannula for 90 seconds.
8 „ „ 89 „

With doses of the $\frac{1}{100}$ cub. centim. (= 0·0086 grm.; NO_2 = 0·00378 grm.) the fall of pressure averaged 49 millims., placing the drug high in the list of the bodies examined. Slightly stronger than iso-butyl nitrite, it was much beyond primary butyl nitrite and α-amyl nitrite in its activity. The reduction of pressure is succeeded by a slower rise, so that after a lapse of 5 minutes from the commencement of inhalation there is frequently a deficiency of 11 or 12 millims. when contrasted with the original pressure. The acceleration of the pulse is greater than after iso-butyl nitrite.

Intra-vascular Injection.—The *intra-vascular injection* of tertiary butyl nitrite in doses of $\frac{1}{100}$ cub. centim. was found on examination to fall far short of inhalation in the extent to which it produces a fall of pressure, so much so that it is much feebler than secondary butyl nitrite, and slightly feebler than the iso-butyl compound. It is also weaker than tertiary amyl nitrite, but retains its superiority over normal butyl nitrite.

But though the fall of pressure is from 35 to 40 per cent. less than after inhalation of a like dose, the reduction of pressure is frequently maintained for a considerable time.

The pulse is accelerated to a less extent than after inhalation averaging six beats per minute, but the acceleration commences from 5 to 8 seconds later after injection than after inhalation.

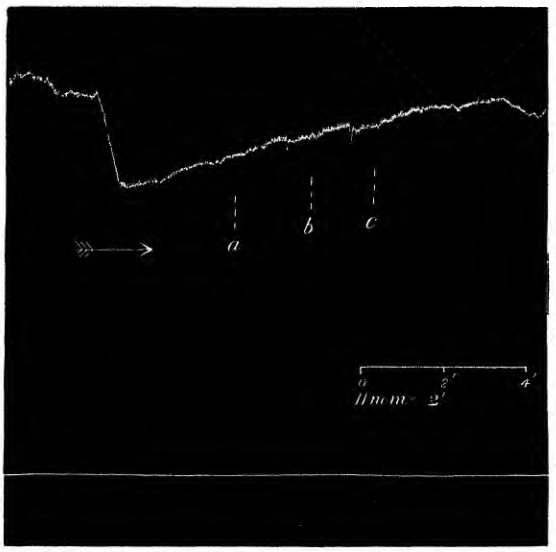
In this respect it stands close to iso-butyl nitrite. The following may be taken as the usual variations of pulse and blood-pressure due to the injection of the $\frac{1}{100}$ cub. centim. of this drug.

Cat of 5 lbs. Etherized. Administered $\frac{1}{100}$ cub. centim. in 5 cub. centim. salt solution. Pressure fell 24 millims. in 5 minutes is −9, in 7·45 minutes is normal. Tracing 12.

	Time.	Pulse.
	secs.	
Before drug	0	148
During injection of $\frac{1}{100}$ cub. centim. tertiary butyl nitrite into femoral vein	5	149
	15	147
	20	148
	25	149
	30	151
	40	154
	50	154
	70	147
	90	147
	110	145
	180	148

As has been already stated the respiration is retarded, or even temporarily suspended, by inhalation of this nitrite (see tracing 10*b*).

Tracing 12.



Injection by femoral vein of $\frac{1}{100}$ cub. centim. iso-butyl nitrite in 5 cub. centim. salt solution.

The Propyl Nitrites.

Primary propyl and secondary propyl nitrites were examined.

Primary Propyl Nitrite.

The most obvious fact concerning primary propyl nitrite is the small degree of activity it possesses in reducing blood-pressure, when contrasted with many of the nitrites already examined. It is very inferior in its effect to the secondary compound, which is amongst the most active of the nitrites. The fall it occasions is not rapid,

the lowest point being reached in from 33 to 38 seconds after inhalation commenced. Recovery to the original level takes place somewhat sooner than the recovery succeeding secondary propyl nitrite, although the latter occasions a much greater fall.

The recovery after pure amyl nitrite in contrast experiments was shown to be slower. Slight retardation of the pulse during early primary nitrite of propyl inhalation is a frequent preliminary to the succeeding acceleration. This acceleration, after doses of $\frac{1}{30}$ to $\frac{1}{40}$ cub. centim., amounts to from 8 to 12 beats per minute. The chief acceleration occurs immediately after the greatest reduction of pressure, *i.e.*, about 40 seconds after the inhalation is begun.

In from $2\frac{1}{2}$ to 3 minutes the pulse usually reaches its original rate or falls below it.

Experiment.—Small cat of 4 lbs. Ether steadily given from ether bottle. Artificial respiration.

Before inhalation, pressure 104; fell on administration of $\frac{1}{38}$ cub. centim. (= 0·0234 grm.; NO_2 = 0·0121 grm.) to 72, and regained the original level in course of 5 minutes. The lowest pressure was in 32 seconds after inhalation was begun.

	Time.	Pulse.
	secs.	
Before inhalation	..	171
After inhalation	10	169
	20	170
	30	177
	40	179
	50	180
	60	180
	70	176
	80	174
	95	174
	145	174
	165	170
	175	168
	185	166

Doses of $\frac{1}{100}$ cub. centim. do not fail to cause a fall of pressure, and here it may be remarked how surprising it is that so small a variation exists in the reaction shown by animals to such widely different doses as the $\frac{1}{30}$ and $\frac{1}{100}$ cub. centim.; the smaller often coming near in its action to the larger dose.

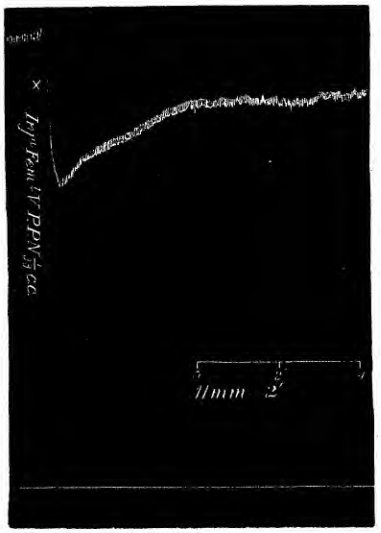
Inhalation of $\frac{1}{100}$ cub. centim. (= 0·0089 grm.; NO_2 = 0·0046 grm.) causes an average fall of 18·5 millims. accompanied by a pulse acceleration of about 3 to 6 beats per minute, while the pressure recovered within the exceptionally short time of three minutes from commencing inhalation. These figures enable us to classify primary propyl nitrite as one of the least active in reducing pressure and in maintaining the reduction, while they indicate only a feeble tendency to produce acceleration.

Intra-vascular Injection.—The relatively feeble effect which this drug produces on inhalation does not fully extend to administration by intra-vascular injection.*

Intra-venous Injection causes a slight rise of pressure, succeeded by a rapid, extensive fall, and a gradual recovery.

The following experiment will serve to illustrate the points under consideration, tracing 13*a*.

Tracing 13*a*.



Injection by saphenous vein of $\frac{1}{38}$ cub. centim. primary propyl nitrite in 5 cub. centims. salt solution.

Tracing 13*b*.

Injection by cranial end of carotid artery of $\frac{1}{38}$ cub. centim. primary propyl nitrite in 2 cub. centims. salt solution.

Injection of primary propyl nitrite $\frac{1}{38}$ cub. centim. in 5 cub. centims. salt solution by saphenous vein.

Original pressure 118·5 millims.

After injection rises in 8 seconds to 122.

Falls in 45 seconds to 81.

In	2	minutes	has risen to	92
,,	4	,,	,,	100
,,	8	,,	,,	102
,,	10	,,	,,	105

* Reference must be made to the section dealing with pure amyl nitrite for the mode of administration.

	Time.	Pulse.
	secs.	
Before injection . . .	..	156
During „ . . .	20	155
After „	5	155
	20	155
	40	154
	60	152
	120	152
	200	152
	240	150
	280	153

Intra-venous Injection of $\frac{1}{100}$ cub. centim. The administration of this small dose causes a fall of pressure slightly superior to that due to inhalation, but the difference is not marked.

The fall averages 20 millims., and the return to the normal pressure is later in occurring, so that in 5 minutes it is usually 4·5 millims. below the normal. This slow rise is accompanied by only a very slight pulse acceleration, if any, the average not exceeding two per minute.

3.3.90.—Cat of 5 lbs. Cannula in femoral vein, &c. Steady inhalation of ether. $\frac{1}{100}$ cub. centim. primary propyl nitrite in 5 cub. centims. salt solution injected into femoral vein. Pressure fell 19 millims.; in 6 minutes it is — 4.

	Time.	Pulse.
	secs.	
Normal	..	126
Injection	5	126
	10	124
	15	125
	20	126
	30	125
	40	126
	60	126
	180	126

Intra-arterial Injection. (Cranial end of carotid.)—This method of administration caused a powerful rise, succeeded by a gradual fall. The pressure recovered comparatively soon. Tracing 13*b*.

Experiment.—Injection into cranial end of carotid artery of $\frac{1}{38}$ cub. centim. primary propyl nitrite in 2 cub. centims. salt solution.

Original pressure was 110 millims.

On injection pressure rose in 33 seconds to 124
,, ,, fell ,, 70 ,, ,, 91
,, ,, rose ,, 120 ,, ,, 101·5
,, ,, ,, ,, 240 ,, ,, 108

	Time.	Pulse.
	secs.	
Before injection. . . .	0	156
During injection of $\frac{1}{32}$ cub. centim. of primary propyl nitrite	20	157
After injection	30	157
	40	155
	65	156
	100	154
	115	152
	140	153
	200	154

In each of these experiments the pulse had little or no tendency to accelerate. The intra-arterial injection was immediately followed by a strong rigor, which had not been produced by other nitrites injected in this manner. The relationship of the action of the drug administered by injection into the vessels and by inhalation is not parallel here with the relationship existing in the case of pure amyl nitrite and of iso-butyl nitrite respectively.

Effect on Respiration.—Although the inhalation of primary propyl nitrite may cause some retardation of respiration, the marked effect occasioned by the butyl compounds has not been observed.

Secondary or Iso-Propyl Nitrite.

This substance when administered by inhalation is one of the most active members of the series in its power of reducing pressure. The fall recorded by the manometer is both rapid and extensive, so that after an inhalation of $\frac{1}{100}$ cub. centim. a reduction of pressure somewhat exceeding that of the iso-butyl nitrite (the latter being usually almost identical with that of secondary butyl nitrite) is observed; for this dose the fall averages about 50 millims.

The speed of reduction is considerable, the lowest pressure being reached in 30 to 35 seconds after the commencement of inhalation. The greater part of the reduction is, however, accomplished during the first 20 seconds, while in the last 10 seconds the decline is scarcely perceptible. The percentage speed of the fall in two observations taken from one experiment averages as follows :—

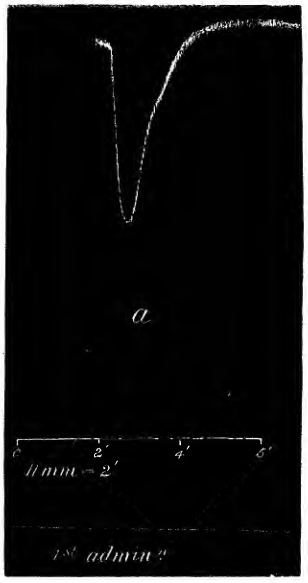
Usual preparation for experiment. $\frac{1}{30}$ cub. centim. (= 0·029 grm.; NO_2 = ·0045 grm.) secondary propyl nitrite administered by inhalation. The fall began in 4·5 seconds.

In the ensuing 10 seconds fall = 57·5 per cent. of the total reduction.
„ 10 „ (20) „ = 30 „ „
„ 10 „ (30) „ = 12 „ „

The fall was therefore practically at an end by the 35th second. In this rapidity of action iso-propyl is not far removed from iso-butyl nitrite, though, as already stated, a close comparison of the effects of the two bodies shows the latter to be somewhat less powerful as a reducer of pressure.

Another point of resemblance lies in the fact that the recovery of pressure is rapidly brought about by the return of tone in the arterioles, with or without a marked acceleration in pulse rate. The rise of pressure towards the normal is at first rapidly accomplished, but after repeated administrations without the production of a serious permanent fall of pressure, the recovery of the normal pressure becomes much more gradual after the administration of the nitrite.

Tracing 14*a*.



Secondary propyl nitrite $\frac{1}{100}$ cub. centim. First inhalation.

Tracing 14*b*.

40 minutes later, the sixth administration.

Tracing 14*c*.

52 minutes later than 14*b*, the eleventh administration.

The following Table gives the results of three administrations of secondary nitrite of propyl in an experiment in which no other nitrite was given.

Time.	Dose.	Fall of pressure.	Period of recovery of pressure.
	cub. centim.	millims.	secs.
(1st administration)	$\frac{1}{100}$	47	109
a 5 minutes			
(6th administration)	„	40	153
f 40 minutes			
(11th administration)	„	42	228
K 92 minutes			reached — 8 and did not rise higher

It will be observed that, after repeated administration, the later part of the recovery of pressure is affected rather than the earlier part, but this may also become retarded. During the inhalation of the drug retardation is a frequent first effect, especially if the original rate is rapid. Subsequent acceleration is by no means extensive; it averages 4 beats per minute after administration of $\frac{1}{100}$ cub. centim. Increase of dose causes a further acceleration (7 beats per minute after $\frac{1}{30}$ cub. centim.), and somewhat increases the fall and retards the rise of pressure.

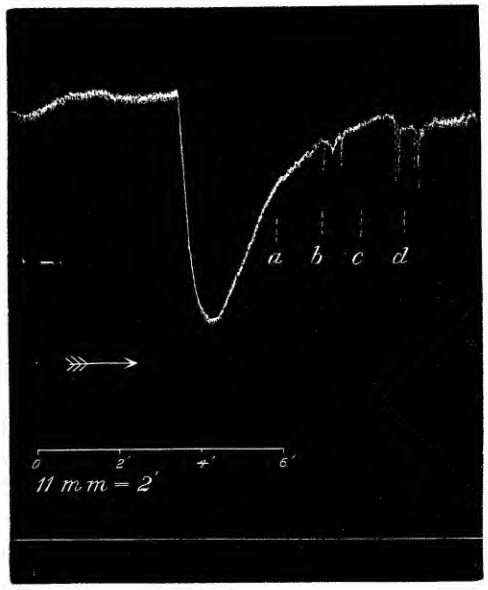
The powerful pressure-reducing effect of secondary propyl nitrite when administered by inhalation is not equalled by that observed after injection into the vessels, although its relative effect is sufficient to place it near the head of the list. After an injection of $\frac{1}{30}$ cub. centim. (= 0·029 grm.; NO_2 = 0·0150 grm.), the average fall is 43 millims.; while after a dose of $\frac{1}{100}$ cub. centim. (0·087 grm.; NO_2 = 0·0045 grm.) it is from 30 to 33, the first indication of reduction being observed in 11 seconds, the minimal pressure occurring in 50 seconds, the injection being completed in 18 to 20 seconds.

The following experiment contrasts the effect of inhalation and injection :—

24.2.90. Cat of 5 lbs. Usual preparation. Receiving ether steadily. Pressure fell 60 millims.; in 5 minutes was — 3. Tracing 15*a*.

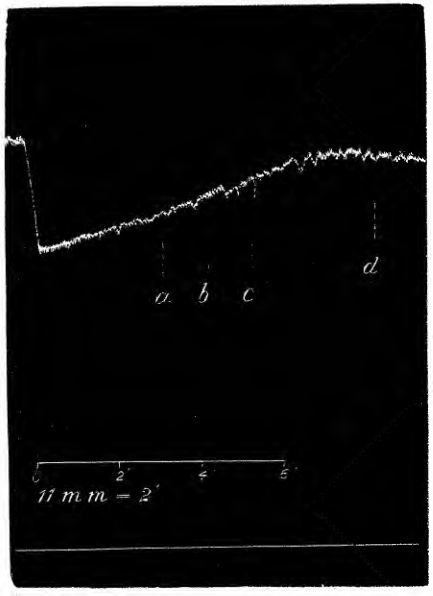
	Time.	Pulse.	Respiration.
	secs.		
Before inhalation	0	134	32
Began inhalation of $\frac{1}{30}$ cub. centim. (= 0·0108 grm.; NO_2 = 0·057 grm.) secondary propyl nitrite	5	132	
	15	133	
	25	132	32
	90	127	31
	420	125	33
	520	136	34

Tracing 15*a*.



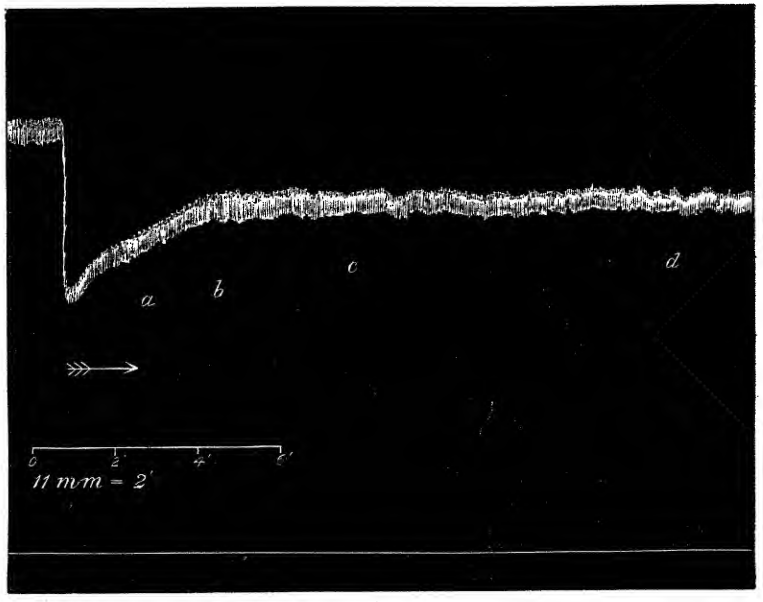
Inhalation of $\frac{1}{80}$ cub. centim. secondary propyl nitrite.

Tracing 15*b*.



Injection into femoral vein of $\frac{1}{100}$ cub. centim. secondary propyl nitrite.

Tracing 16.



Injection by femoral vein of $\frac{1}{80}$ cub. centim. secondary propyl nitrite.

Tracing 17

Inhalation of $\frac{1}{80}$ cub. centim. secondary propyl nitrite. Reduced one-half, preceded and accompanied by stimulation of the central end of the sciatic nerve. The upper line shows pulse and pressure, the middle respiration, the lowest shows signal record of time of stimulation. See also pressure record taken on slow drum.

24.2.90. *Intra-venous Injection.*—Pressure fell 30 millims.; in 7 minutes 16 seconds was — 4 millims. Tracing 15*b*.

	Time.	Pulse.	Respiration.
	secs.		
Before administration	0	124	32
Injected $\frac{1}{100}$ cub. centim. secondary propyl nitrite into femoral vein .	5	123	
	15	118	
	20	117	
	45	123	
	70	123	34
	85	120	
	95	120	31
	180	105	35
	240	104	
	300	101	31

A larger dose of secondary propyl nitrite given by injection causes a moderate primary fall. The recovery after this may be tolerably rapid at first, but subsequently the pressure rises very slowly, so that it is often a considerable time before the original level is reached.

13.2.90. Cat of medium size. Steadily etherized. Usual preparation. Inhalation of $\frac{1}{80}$ cub. centim. secondary propyl nitrite, having occasioned a fall of 54 millims. Almost complete recovery in 5 minutes.

An injection of $\frac{1}{30}$ cub. centim. secondary propyl nitrite in 5 cub. centims. salt solution was made into the femoral vein. Tracing 16.

The pressure fell 45 millims.

In 4 minutes was 21 millims. below the original level.
„ 5 „ „ 21 „ „ „ „
„ 8 „ „ 19 „ „ „ „
„ 10 „ „ 19 „ „ „ „

The pressure remained permanently reduced.

	Time.	Pulse.
	secs.	
Before	0	123
During injection of $\frac{1}{80}$ cub. centim. secondary propyl nitrite	5	122
	10	120
	20	119
	10	117
	15	
	20	122
	30	123
	40	
	50	
	75	122
	420	114
	900	116

Respiration.—The effect of a single administration of secondary propyl nitrite is first to retard, then to accelerate the respiration; this phase is succeeded by a period during which acceleration without any retardation results, and this, again, is succeeded by a tendency to considerable retardation, when the administration has been frequently repeated. The effect produced on respiration by this body is much less marked than that of the butyl compounds.

If in the early stage of retardation produced during the first administration the central end of the sciatic nerve is strongly stimulated, acceleration and deepening of the respiration results; but the fall of the pressure is not prevented, not even diminished. Here it is interesting to observe that the respiratory centre does not cease to respond to the stimulation until a distinct fall of pressure has taken place.

(19.6.90.) Cat of 5 lbs. Steadily etherized. Breathing rapid throughout. Tracing 17.

On inhalation pressure fell 122–84 (38 millims.), in 196 seconds is normal and passes slightly beyond it, so that in 5 minutes it is 124 millims.

	Time.	Pulse.	Respiration.
	secs.		
Before inhalation	..	186	52
Sciatic stimulation	0	187	75
Sciatic stimulation and inhalation of secondary propyl nitrite, $\frac{1}{80}$ cub. centim.	5	186	84
	10	180	
Stimulation ended	20	178	75
	30	177	
	40	183	42
	50	183	46
	60	189	45
	80	187	45

Ethyl Nitrite.

Since the manipulation of this substance is attended with no small difficulty because of its low boiling point (17° C.), the bottle, pipette, and tube into which the nitrite was carried were thoroughly cooled with ice.

The drug was usually introduced into a cooled bulb with tubing at both ends closed by screw clamps. The tubing was brought into connection with the inhalation apparatus, a water valve being placed distally in relation to it, and the tracheal cannula valve permitting only of expiration was employed as usual.

Its action was tested in experiments in which it was used alone as well as in other experiments in which other nitrites were also used, whose position had been approximately ascertained.

Ethyl Nitrite by Inhalation.—This nitrite when administered by inhalation is not found, as regards its power of reducing pressure, to be a prominent member of the nitrite series.

With doses of $\frac{1}{100}$ cub. centim. (= 0·0089 grm.; NO_2 = 0·00545 grm.) the average fall in pressure is between 19 and 20 millims., and the chief reduction is brought about in 25 to 28 seconds after the commencement of inhalation.

The most usual mode of return towards the normal is by a gradual elevation of pressure which approaches the normal in 6 to 8 minutes, but in exceptional cases a more rapid reaction ensues and an equal amount of recovery may occur in 3 minutes. In the latter case the variation is not due to a greater acceleration of pulse or any change in respiration.

As a rule acceleration of the pulse occurs up to 7 per minute, and it is not long maintained. The respiration is retarded. Larger doses, viz., the $\frac{1}{40}$ cub. centim. to $\frac{1}{30}$ cub. centim. given by inhalation increase to some extent the fall of pressure, and tend, as in smaller doses, to produce a prolonged reduction of pressure. In exceptional cases the return is more active, thereby resembling the effect of a smaller dose of iso-butyl nitrite.

One such result may be quoted.

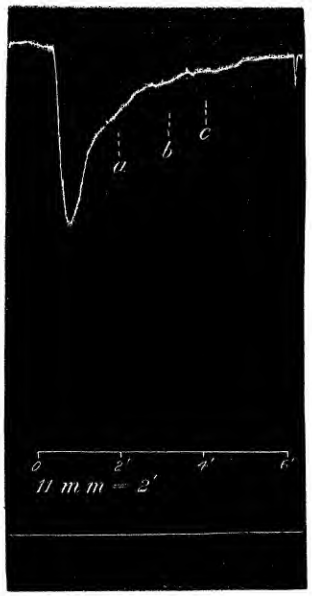
(17.3.90.)—Cat of 4½ lbs. Steadily etherized. Tracing 18.

On inhalation of $\frac{1}{34}$ cub. centim. (= 0·0261 grm.; NO_2 = 0·0160 grm.) of the ethyl nitrite, the pressure fell 44 millims. (127 to 83); in 120 seconds it rose again to 119 millims., and in 196 seconds to 122 millims. or within 5 millims of the normal. The initial fall was observed 5 seconds after the commencement of inhalation, and the lowest point was reached in 25 to 30 seconds, a rise immediately occurring.

The course of the pulse and respiration may be traced from the following figures.

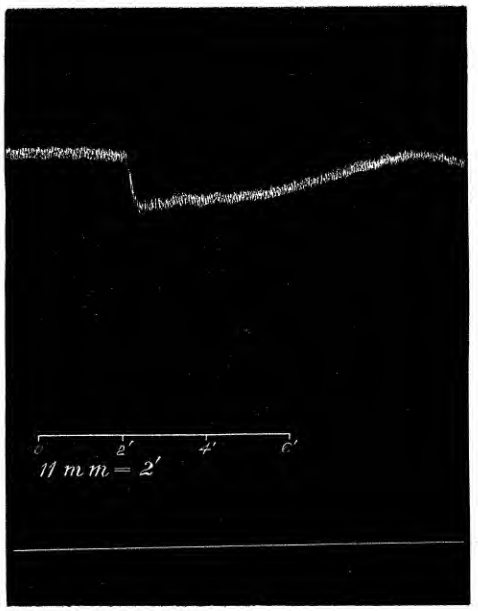
	Time.	Pulse.	Respiration.
	secs.		
Before inhalation . . .	..	135	33
Inhalation of $\frac{1}{34}$ cub. centim. commenced	0		
	5	136	31·5
	10	138	
	15	138	
	20	138	27
	30	137	
	40	135	
	50	133	27
	60	132	
	90	111	22
	160	117	22
	220	122	25

Tracing 18.



Inhalation of $\frac{1}{34}$ cub. centim. ethyl nitrite.

Tracing 19.



Inhalation of $\frac{1}{50}$ cub. centim. ethyl nitrite.

During inhalation of the smaller dose a slight retardation of the pulse is frequently noticed, and occasionally the pulse remains subnormal throughout; but usually this phase of slowing is only of short duration, and is succeeded by a slight acceleration, which reaches its maximum about 35 seconds after the commencement of inhalation.

This increase may be to the extent of 6 to 10 beats, and the respiration appears to be slowed at first, and, like the pressure, recovers itself gradually.

We will now give an illustration of the prolonged reduction of pressure which has been frequently observed. In this case the primary reduction of pressure was decidedly below the average.

(31.5.90.) Cat of 7 lbs. Receiving ether regularly. Vagi intact. Breathing natural. Tracing 19.

Blood-pressure 104. Pulse 154. Respiration 25·5.

Administered $\frac{1}{50}$ cub. centim. (= 0·0178 grm.; NO_2 = 0·0109 grm.) ethyl nitrite.

Pressure began to fall in 4 seconds; fell to 90 millims. in 30 to 35 seconds.

In 2 minutes it rose to 92 millims.
,, 4 ,, ,, 96 ,,
,, 6 ,, ,, 100·5 ,,

	Time.	Pulse.	Respiration.
	secs.		
Before inhalation . . .	..	156	23·5
Inhalation	0		
	5	156	22·5
	10	156	
	20	153	24·5
	25	154	
	30	160	17
	35	158	
	40	156	
	45	156	
	50	156	19·5
	55	156	20
	100	156	21·5
	110	..	22·5
	140	158	24
	360	159	24

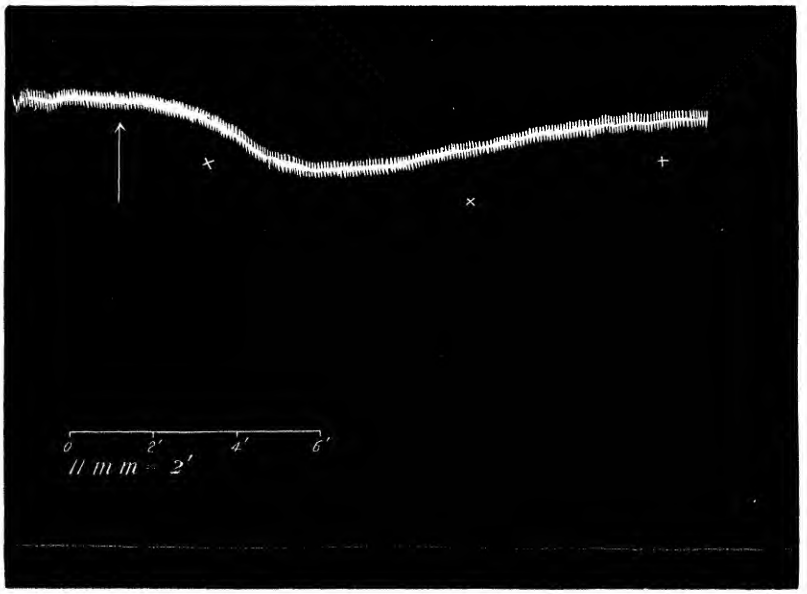
It will be observed in this experiment that a marked retardation of respiration followed inhalation, but there was a return to the normal in 2 minutes.

Ethyl nitrite administered by (*a*) hypodermic and (*b*) by intra-vascular injection.

(17.7.90.) (*a*) *Hypodermic Injection.*—The absorption of the nitrite when injected beneath the skin of the flank proceeds with considerable rapidity. In the experiment quoted, a distinct fall of pressure was observed 49 seconds after the injection of $\frac{1}{50}$ cub. centim. commenced. The time occupied by the injection was 20 seconds. The lowest point was reached 3 minutes later. Tracing 20.

Original pressure 118 millims.
3 minutes fell to 107 ,,
4·5 ,, ,, ,, 100 ,,
8 ,, rose to 106 ,,
12 ,, ,, ,, 112 ,,
14 ,, ,, ,, 113·5 ,,

Tracing 20.



Hypodermic injection of $\frac{1}{50}$ cub. centim. ethyl nitrite.

	Time.	Pulse.
	secs.	
Original pulse rate	..	140
During injection	20	140
After injection completed . . .	10	136
	20	136
	30	136
	40	139
	50	139
	60	139
	70	138
	110	139
	130	134
	140	133
	150	132
	400	132
	580	137
	740	141

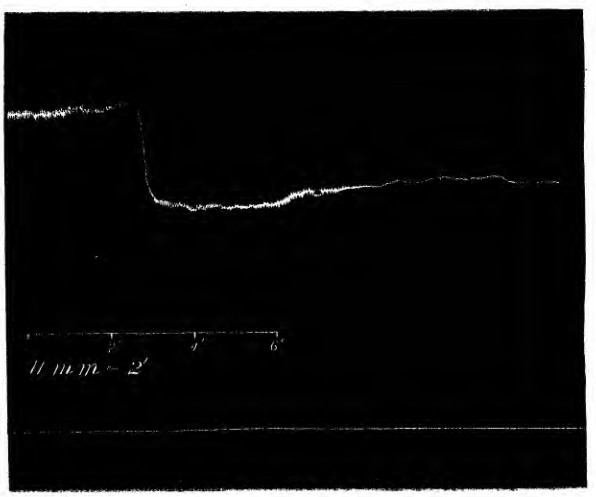
Intra-vascular Injection.—The fall after this method of administration is prompt and extensive, and a prolonged subnormal level of the pressure ensues during which the rise is very gradual.

By intra-venous injection a powerful effect may be produced on respiration, causing its temporary arrest, or, if the dose be larger, its permanent suspension. (After one administration a singular effect was observed. The blood-pressure had fallen 28 millims. after injection of $\frac{1}{38}$ cub. centim. ethyl nitrite, and remained at this level; respiration became rapidly feeble and ceased; the pressure fell still further in spite of artificial respiration, no tendency to spontaneous respiration appearing

5 minutes after the injection. When the vagi were divided the pressure rose and respiration was immediately resumed.)

An experiment will now be quoted which illustrates the usual effect of injection.

Tracing 21.



Intra-venous injection of $\frac{1}{38}$ cub. centim. ethyl nitrite.

(4.6.90.)—Cat of $5\frac{1}{4}$ lbs. Steadily etherized. Cannulæ in carotid artery and saphenous vein. Original pressure 86, after injection of $\frac{1}{38}$ cub. centim. (= 0·0234 grm.; NO_2 = 0·0143 grm.) ethyl nitrite by saphenous vein, fell to 60 millims. Tracing 21.

In 2 minutes pressure was 59 millims.
„ 4 „ „ „ 62·5 „
„ 6 „ „ „ 65 „

	Time.	Pulse.
	secs.	
Before injection	..	161
During „	25	159 to 156
After „	15	154
	30	155
	50	154
	80	154
	110	154
	140	150
	230	155
	300	155

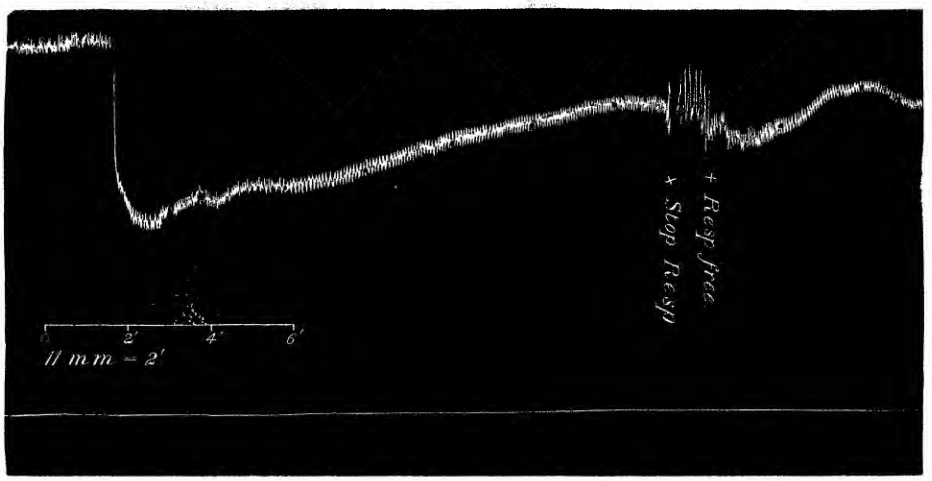
In this experiment the initial reduction in pressure was preserved for a considerable time.

It is also seen that a decided fall in the pulse rate was associated with the action

of this drug after intra-venous injection, although in two minutes afterwards there was a feeble return towards the normal.

Another case in which a larger dose was given may be contrasted with the experiments in which the administration was by inhalation.

Tracing 22.



Injection of $\frac{1}{18}$ cub. centim. ethyl nitrite in 5 cub. centims. salt solution into femoral vein. Showing effect of suspending respiration.

(31.5.90.) Injection of $\frac{1}{38}$ cub. centim. (= 0·0488 grm.; NO_2 = 0·0302 grm.) ethyl nitrite in 5 cub. centims. salt solution into femoral vein. Tracing 22.

Pressure originally 100 fell to 51 (= 49) millims.

In	2	minutes	the pressure was	58
,,	4	,,	,, ,,	60·5
,,	6	,,	,, ,,	64
,,	8	,,	,, ,,	71
,,	10	,,	,, ,,	77
,,	12	,,	,, ,,	81
,,	16	,,	,, ,,	84

Arrest of respiration caused large waves in the pressure, but no permanent rise of pressure.

	Time.	Pulse.	Respiration.
	secs.		
Before injection	..	144	27
During injection of $\frac{1}{18}$ cub. centim. (= 0·0556 grm.; NO_2 = 0·034 grm.) ethyl nitrite into saphenous vein	0 10	144	27
Injection ended	20	142	22
	30	138	15
	40	136	15
	50	140	15
	65	144	Respiration becoming very rapid.
	70		
	80	138	
	95	144	16·5
			Very faint.
	105	..	No respiration.
	125	..	4
	140	..	4·5
	180	..	9

The fall of pressure commenced 12 seconds after injection, and attained its lowest point in 55 seconds. The lasting retardation of respiration played an important part in the prolonged reduction of pressure.

One cannot but assign to the nitrite of ethyl a peculiar place among the other substances of the series examined. When given by inhalation the fall of blood-pressure, although inconsiderable, is frequently of prolonged duration. When injected subcutaneously the fall is distinct and enduring, whilst after intra-venous injection there is a prompt fall associated with even slower recovery of pressure and usually with retardation of pulse.

Methyl Nitrite.

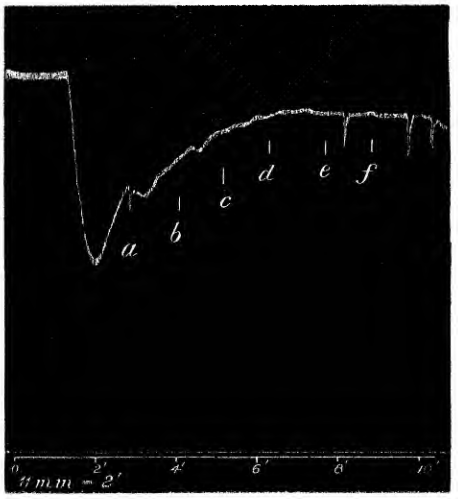
Methyl nitrite was employed in this series of experiments in the gaseous form. It was introduced, as has been already explained, at the temperature and pressure noted into spindle-shaped glass bulbs, the ends of which were drawn out into fine points. Such bulbs were prepared for experimental use by drawing over their ends rubber tubes provided with clamps, securing them by ligatures, and connecting them with the lateral inhalation tube and the water-valve bottle. The thin glass ends were fractured inside the rubber tubes when all was ready for inhalation ; the clamps opened, and, last of all, the stopcock proximal to the animal turned on at the same instant as the ether bottle or air tube, as the case might be, was turned off. The bulb and system of tubes were rapidly emptied of the nitrite, and the fall of blood-pressure promptly ensued. By this method, measured quantities of nitrite were administered with perfect precision.

In all cases the primary fall of pressure was well marked, though not of great extent when contrasted with the effect of a comparative dose of many other nitrites.

Usually, there was a considerable pause before the normal pressure was recovered, the return being only gradually accomplished. (The return in the experiment first quoted was unusually rapid.) Acceleration of the pulse was not a prominent feature in the action of methyl nitrite; three to four beats per minute was frequently the full amount of acceleration induced by about $\frac{1}{50}$ cub. centim. of the liquid nitrite. A great retardation of the pulse was observed in a large precentage of cases of inhalation, whilst the breathing was affected in a similar manner. Several inhalations terminated fatally.

Some experiments showing the results of inhalation will now be described.

Tracing 23*a*.



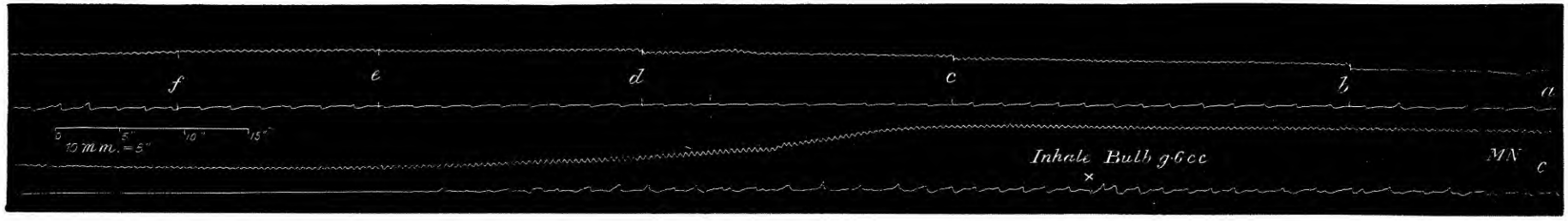
Inhalation of 0·0245 grm. methyl nitrite, the letters correspond to those in the quick tracing 23*b*.

Experiment.—Large cat. Steadily etherized. Tracings 23*a* and 23*b*. Administered 9·6 cub. centims. bulb of methyl nitrite from tracheal cannula (= $\frac{1}{35}$ cub. centim. liquid) (= 0·0245 grm.; NO_2 = ·0185 grm.).

Original pressure, 98 millims., fell to 48 = fall of 50 millims.

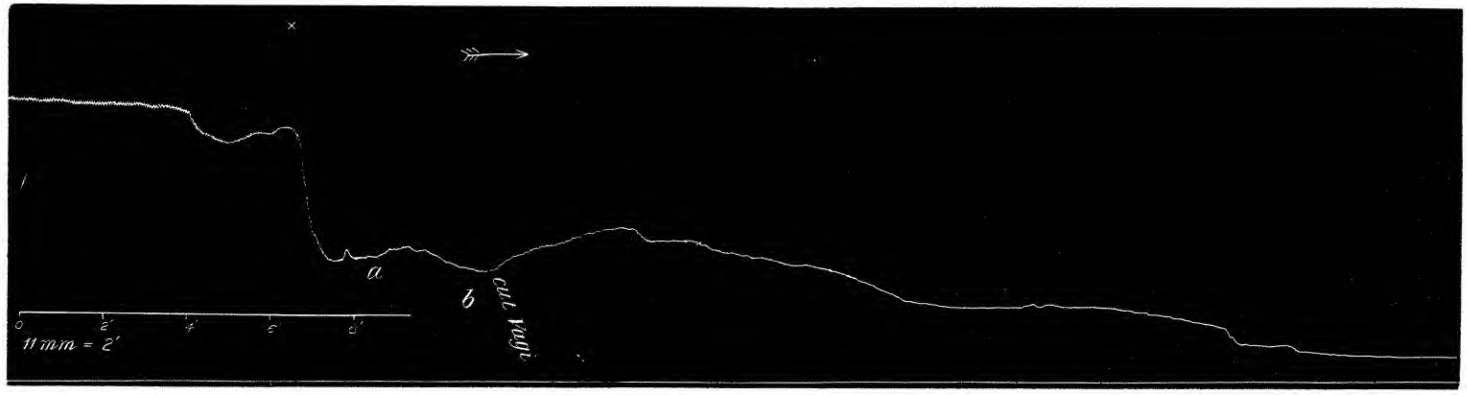
In 2 minutes	rose to	67	millims.
,, 4	,,	,,	86	,,
,, 6	,,	,,	89	,,
,, 8	,,	it was	88	,,

Tracing 23*b*.



Inhalation of methyl nitrite (9·6 cub. centims. bulb). Reduced one-half. The upper tracing is continuous with the lower. The upper line in each pair shows pressure and pulse; the lower respiration. The letters correspond with those on the slow tracing 23*a*.

Tracing 24.



Inhalation of methyl nitrite (10 cub. centims. bulb) at star. The vagi are cut where indicated. This record is taken on the slow cylinder by a mercurial manometer, and is to be read from left to right.

	Time.	Pulse.	Respiration.	
	seconds.			
Before inhalation . . .	..	130	33	
Methyl nitrite 9·6 cub. centims. bulb, inhalation begun, molecular equivalent to $\frac{1}{35}$ cub. centim. (liquid)	0			
	5	131		
	10	132	33	
	20	132		
	25	135	21	
	35	135	27	
	40	135	..	Breathing irregular
	45	133	..	Breathing stopped
	55	128		
	65	124		
	75	..	..	Breathing recovered
	87	122	23	
	160	128	20	
	230	127		
	300	128	27	
	360	112	26	
	450	112	28	

The slowing of respiration leading to entire suspension is here a noticeable effect. The pause was only temporary, and terminated after 30 seconds, the respiration resuming a fairly rapid rhythm.

The result of inhalation next recorded shows the alternative form of recovery. It indicates a slighter primary effect than the last, succeeded by a slow but gradual return of pressure.

Experiment.—(2.) Medium sized cat. Steadily etherized. Administration of 10·2 cub. centims. bulb, equivalent to $\frac{1}{37}$ cub. centim. of liquid (= ·0261 grm.; NO_2 = ·0196 grm.). Bulb connected with inspiratory apparatus; administration as in preceding experiment.

Original pressure 142 fell to 106 millims., fall of 36 millims.

In	4	minutes	pressure was	108	millims.
,,	6	,,	,, ,,	116	,,
,,	8	,,	,, ,,	124	,,
,,	$10\frac{1}{2}$	,,	,, ,,	136	,,
,,	13	,,	,, ,,	139	,,
,,	15	,,	,, ,,	141·5	,,

	Time.	Pulse.
	secs.	
Before inhalation	..	153
Inhalation begun	0	
	5	156
	10	
	15	158
	20	159
	25	156
	30	153
	35	
	55	150
	75	
	95	147
	130	143
	240	143
	360	140
	480	147

The following is an example of the experiments already referred to in which inhalations terminated fatally.

(14.3.90.) Half-grown cat. Usual preparation. Steadily etherized. Administration of 10 cub. centims. bulb (= ·0256 grm. ; NO_2 = ·0192 grm.). Bulb in connection with respiratory apparatus, water-valves, &c. Tracing 24.

On inhalation the pressure fell from 67 to 32 millims., in 120 seconds it rose to 35 and in 15 seconds more to 36 ; it then declined until the vagi were divided (at 284 seconds) when it rose to 41, but thereafter declined steadily, death resulting in spite of artificial respiration.

	Time.	Pulse.	Respiration.
	secs.		
Before inhalation	..	138	14
Inhalation begun	0		
	5	138	
	10	136	14·5
	25	136	
	30	137	
	40	139	
	50	138	
	65	139	16
	85	140	
	145	..	14
	220	80	2
Vagi divided	287		
	330	74	
	390	..	Artif. resp.

Although artificial respiration was had recourse to the action of the heart gradually became feebler, and the pressure having fallen to 22 millims. 14 minutes 30 seconds

after inhalation commenced, artificial respiration was suspended, and death ensued. There need be no doubt that such a dose is a dangerous one, even for a fully grown animal.

In one instance inhalation of a 5 cub. centims. bulb (= ·0178 grm. ; NO_2 = ·0096 grm.) nearly proved fatal.

In this experiment made upon a cat of $6\frac{3}{4}$ lbs. the pressure fell at once 50 millims. (98 to 48 millims.), the frequency of the pulse was reduced one-half in 55 seconds, viz., from 139 to 67, two or three beats occurring in groups succeeded by a long diastolic pause. The respiration, after four or five deep breaths had been taken, was reduced to an occasional gasp. Artificial respiration was used and the vagi divided ; but gasping occurred after, just as before vagotomy. The pulse which had increased to 96 under artificial respiration rose 4 beats more when the vagi were divided. The pressure never rose higher than 66 millims., and thereafter gradually declined 35 minutes after inhalation, to 34 millims., when another small dose of methyl nitrite caused cardiac arrest.

Intra-vascular Injection of Gaseous Methyl Nitrite.—By connecting a bulb containing a given volume of methyl nitrite with the rubber tubing tied on the femoral vein cannula, which had been previously filled with salt solution, and forcing out the gas before salt solution discharged from a syringe into the other end of the bulb, it became a simple matter to introduce the nitrite into the femoral vein, and so to study its action.

All such injections terminated fatally, even though they were made very gradually. Although no gas bubbles could be detected in the right side of the heart, the fatal result was very probably, in some measure, due to embolism. Larger quantities of atmospheric air were, however, injected at the same slow rate into the central end of the vein without death resulting.

A marked retardation of the pulse preceded the fatal action of the drug, but in no case was an abrupt arrest of the heart witnessed.

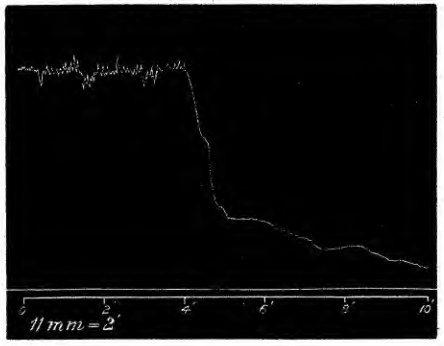
(14.3.90.) Cat of $4\frac{1}{2}$ lbs. Etherized—usual preparation. (The animal had already had a 10 cub. centims. bulb of methyl nitrite by inhalation, and two administrations of iso-butyl nitrite $\frac{1}{100}$ cub. centim.) A 9 cub. centims. bulb of methyl nitrite was connected with the femoral vein, and injection gradually made at the time indicated.

The original pressure was 59, the pulse 79, and respiration 59. Tracing 25*a* (slow), tracing 25*b* (fast).

On injection the pressure fell to 21, a momentary pause having occurred at 39 seconds.

In 2 minutes pressure was 15 millims.
,, 4 ,, ,, 10 ,,
,, 6 ,, death.

Tracing 25*a*.



Injection of gaseous methyl nitrite into femoral vein. For pulse see quick cylinder tracing 25*b*.

Tracing 25*b*.

Injection by femoral vein of methyl nitrite (9 cub. centims. bulb). (Reduced one-half.) The lowest line records respiration; the stars indicate duration of injection; the middle line is the pulse and pressure; the top line is continuous with the middle one. Owing to contact of the pens in the lowest pair of lines the respiration is not recorded during the latter part of the tracing. For pressure see tracing 25*a* taken upon slow drum.

	Time.	Pulse.	Respiration.
	secs.		
Before injection . . .	0	79	
Slow injection of gaseous methyl nitrite	15	79	Respiration ceased
	25	80	
	35	87	
	45	89	Three faint respirations
	55	87	
	65	87	
	70	79	
	75	53	
	80	52	
	95	46	
	105	46	Artificial respiration commenced
	135	31	
	155	30	Artificial respiration was maintained 4 minutes, but heart gradually failed and then stopped at 6 minutes after inhalation was begun

It would be injudicious to compare too closely the action of this *gaseous* nitrite administered by injection with that of the other *liquid* nitrites, as the necessary data for the comparison cannot be obtained.

The respiration and heart are both profoundly affected by it in the doses indicated. By inhalation also the drug is very active and has a powerful tendency to arrest respiration. The extent to which it lowers the pressure places it above ethyl nitrite, as its average effect is greater.

The reduction of blood-pressure is often prolonged, as has been recorded in the case of the ethyl compound.

Judging from these inhalations in which the pressure was more or less perfectly recovered, the relative position of methyl nitrite to the other bodies examined may be stated as follows:—Its effect in reducing pressure would place it above butyl nitrite and ethyl nitrite, but below tertiary amyl nitrite and the remaining butyl compounds. It most nearly approaches α-amyl nitrite in this respect. The extent of its action appears to be greater than that of the other compounds owing to its depressant effect on the respiration, and frequently also on the heart.

Methyl nitrite has proved lethal in smaller doses than the other nitrites examined.

V.—General Summary of Blood-pressure Experiments.

The chief result of these experiments may be broadly indicated as follows:—

All the nitrites examined produce, in whatever way administered, a reduction of blood-pressure—variable, however, according to the compound employed, in extent and progress as well as in the ensuing recovery.

Acceleration of the pulse usually accompanies and succeeds the fall of pressure on inhalation, the extent of acceleration varying in the individual nitrites. It may be stated that the acceleration is less upon intra-vascular injection—especially when intra-arterial—than after inhalation. A distinct retardation of the pulse is frequently produced when the injection is into the carotid artery.

The extent of acceleration appears to be less in cats than in the human subject. It is probably also less in cats than in dogs, judging from the experiments on the latter recorded by other observers. (In the experiments of others a mixed nitrite of amyl was employed, and the absence of exact information as to the amount inhaled makes it difficult to compare them with the results now described. The question has not been considered of sufficient importance in the present connection to induce us to enter upon it.)

The respiration is affected by the nitrites (1) temporarily during, and immediately subsequent to, inhalation in various degrees, some of them proving much more active than others. (2) It is affected permanently by the repeated administration of the same or of different nitrites. The action of the nitrites in these respects may be contrasted by arranging them in a tabular form according to their activity.

I. *Reduction of Blood-pressure.*

(*a.*) On inhalation.

(*b.*) On intra-vascular injection.

(*a.*) Greatest effect for similar doses (by volume) of the nitrites enumerated, administered by inhalation—

1. Secondary propyl nitrite.
2. Tertiary butyl ,,
3. Secondary butyl ,, } nearly equal.
4. Iso-butyl ,, }
5. Tertiary amyl ,,
6. α-amyl ,, } nearly equal.
7. α- and β-amyl ,, }
8. Methyl ,,
9. Butyl ,,
10. Ethyl ,,
11. Propyl ,,

(*b.*) Greatest effect on intra-vascular (venous) injection.*

1. Secondary butyl nitrite.
2. ,, propyl ,, } nearly equal.
3. Iso-butyl ,, }

* Methyl nitrite invariably caused death when administered by injection in the gaseous form, this result being probably due in part to aerial embolism. If the extent of the first fall were only taken

4. Tertiary butyl nitrite } nearly equal.
5. „ amyl „ }
6. Butyl „
7. α-amyl „
8. α- and β-amyl „
9. Ethyl „ } nearly equal.
10. Propyl „ }

II. *Longest Duration of Subnormal Pressure* after—

(α.) Inhalation of equal quantities by volume of the nitrites.

(b.) Intra-vascular injection of equal quantities by volume of the nitrites.

(α.) *Inhalation.*

1. Methyl nitrite.
2. Ethyl „
3. Tertiary amyl „ } nearly equal.
4. Tertiary butyl „ }
5. Secondary butyl „
6. Butyl „
7. α-amyl „ } nearly equal.
8. α- and β-amyl „ }
9. Iso-butyl „
10. Secondary propyl „
11. Propyl „

(b.) *Intra-venous Injection.**—The following order may be taken as approximately correct, though the rates of return of pressure have not proved so constant in the case of individual nitrites as was the fall of pressure they produced.

1. Ethyl nitrite.
2. Tertiary amyl „
3. α-amyl „ } nearly equal.
4. α- and β-amyl „ }
5. Secondary propyl „
6. Butyl „
7. Tertiary butyl „
8. Secondary butyl „
9. Propyl „ } nearly equal.
10. Iso-butyl „ }

methyl nitrite would stand before ethyl nitrite, and nearly on an equality with α-amyl nitrite. It has been deemed advisable, however, not to introduce it into the series.

* See note on methyl nitrite administered by injection.

III. *Greatest Acceleration of Pulse* after*—

(*a.*) Inhalation.

(*b.*) Injection of equal volumes of the nitrites.

(*a.*) *Inhalation.*

1. Tertiary amyl nitrite.
2. α-amyl ,,
3. α- and β-amyl ,,
4. Tertiary butyl ,,
5. Iso-butyl ,,
6. Secondary butyl ,
7. Butyl ,,
8. Secondary propyl ,,
9. Propyl ,,
10. Methyl ,,
11. Ethyl ,,

(*b.*) *Intra-venous Injection.*†

1. Tertiary amyl nitrite.
2. α-amyl ,,
3. α- and β-amyl ,,
4. Tertiary butyl ,,
5. Secondary butyl ,,
6. Butyl ,,
7. Iso-butyl ,,
8. Secondary propyl ,,
9. Propyl ,,
10. Ethyl ,,

IV. *Action of Nitrites Administered* (A) *by Inhalation on Respiration.*

Amyl Nitrites.—The usual course of the respiration on administering α-amyl nitrite is a slight retardation at the commencement of inhalation, succeeded by an acceleration of 5 to 9 per minute. Frequent administrations tend to cause a lasting retardation. The mixed α and β compounds and the tertiary amyl nitrite cause a very similar effect.

* It will be understood that when retardation of the pulse is produced in place of acceleration, this is caused chiefly by the bodies towards the end of the series.

† Acceleration only occurs with moderate regularity after the nitrites at the upper end of the series (the first three places). Below this point retardation of the pulse becomes more common until, at the lower end, it is a well-marked phenomenon.

Methyl nitrite, though omitted from the list, causes a retardation before death, which would place it below ethyl if the doubtful character of its action did not render its classification unadvisable.

Butyl Nitrite tends to cause a distinct retardation during inhalation, more marked and lasting than in the case of the amyl compounds, and succeeded by less acceleration.

Iso-Butyl as well as secondary butyl and tertiary butyl nitrites cause a very marked slowing, frequently with a pause in respiration. This slowing may last for some minutes after inhalation, or may yield to an acceleration which is rarely so marked as that produced by the amyl compounds. A deepening of respiration follows the early retardation of pause.

Propyl Nitrites do not affect the respiration so much as the butyl compounds. They may produce a little slowing at first, or the respiration may remain unaltered till 30 to 40 seconds after inhalation has commenced, when some acceleration usually results, but this acceleration is more marked after the amyl compounds. The secondary propyl nitrite produces a stronger effect than the primary.

Ethyl Nitrite, in doses which materially reduce the blood-pressure, causes a marked slowing with an occasional tendency to pause. This retardation may last for some time, the respiration becoming somewhat deeper, or it may ultimately yield to a limited acceleration.

Methyl Nitrite acts powerfully in retarding the respiration, and in tending to produce a pause which is often prolonged in character. The respiratory effort appears distinctly weakened by the nitrite, even in absence of the slight degree of acceleration which may occasionally be observed. The gaseous methyl nitrite is probably the most active member of the series in this respect.

Action of Nitrites Administered (B) *by Intra-vascular Injection on Respiration.**

Modification of respiration by the various nitrites is not so readily produced by injection as by inhalation.

The Amyl Nitrites cause an acceleration of 2 to 4 respirations per minute throughout, or exceptionally cause a retardation of 2 or 3 as a preliminary to the acceleration.

The Butyl Nitrites do not produce the initial pause which so frequently follows upon their inhalation, but they occasion a marked slowing of respiration, which usually lasts for 2 minutes, after which it returns to the normal rate, or slightly exceeds it. The tertiary butyl nitrite appears to be most active of the four in causing this alteration.

The Propyl Nitrites influence the respiration but little, a slight acceleration of 3 per minute, and lasting for 90 seconds, is usual after the secondary nitrite. The primary in the doses of $\frac{1}{100}$ to $\frac{1}{50}$ cub. centim. frequently produces no change beyond a retardation or acceleration of 1 per minute.

Ethyl Nitrite.—Considerable slowing of respiration follows the injection of $\frac{1}{18}$ cub. centim. which may amount to 60 per cent. or more of the respirations, and often

* This general statement is submitted in place of the details in the notes of experiments, which it was concluded not to burden with records of slight respiratory changes caused by injection.

persists for some minutes. A smaller dose ($\frac{1}{38}$ cub. centim.) produces a distinct retardation.

Methyl Nitrite renders the respiration irregular and gasping, in 60 seconds the respiratory movement has become faint, and ceases altogether about the time that the heart stops.

The Ethyl and Methyl Nitrites produce a more marked effect on respiration than any other members of the series.

We postpone the consideration of the cause of divergences in the effects produced by the various nitrites to the end of the paper, where they will be discussed in connection with the chemical constitution of these bodies.

VI.—General Consideration of the Modification of Nitrite Action by Splanchnic Stimulation and Section.

The influence of the various nitrites has been studied with the sympathetic nervous system intact; it has also been tested after both splanchnic nerves in the cat had been divided, and during their subsequent stimulation. The complicated nature of the experiment made it difficult to reproduce exactly the conditions of pressure, &c., which would be necessary for an exact comparison of the long series of nitrites examined, attention will therefore be directed to the more general effects produced by these bodies and only the broader distinctions recognisable between them will be indicated.

Division of the splanchnic nerves is attended by a considerable fall of blood-pressure, from this fall of pressure a temporary and partial recovery may, however, occur, and it is clear that there are still agencies in play besides the part capable of modifying the general pressure to a considerable extent. After splanchnectomy all the organic nitrites are capable of causing a still further fall of pressure, though their effect is not so great as before section.

Apart from the peripheral ganglionic plexuses, which, according to some observers, may possibly preserve a certain degree of control after double splanchnectomy, it would be both remarkable and anomalous if changes in the composition of the blood were incapable of producing any alteration upon the relaxed walls of the vessels.

We have no reason for asserting that the dilatation after section of the sympathetic is exactly equivalent to nitrite dilatation. The former is probably not a maximal dilatation, for Ludwig and Cyon found that when they stimulated the depressor nerve after section of both splanchnics the blood-pressure fell still further. It is very possible that the fall of pressure after nitrite inhalation is attributable to changes in the splanchnic area, in addition to the dilatation which undoubtedly occurs in other areas. Brunton found that after section of the cervical cord a reduction of pressure still took place on nitrite inhalation.

If during the continuance of pressure-reduction which follows splanchnectomy the

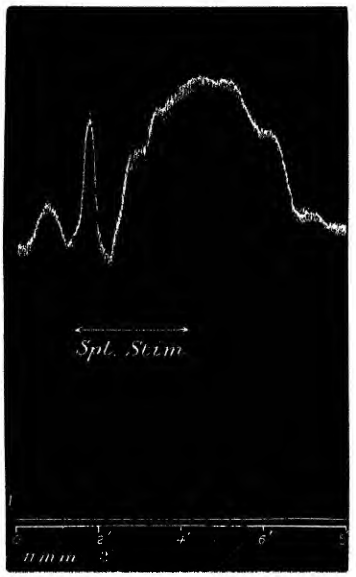
nitrites are administered, the fall, though occurring, is not equal to its previous extent. If, on the other hand, the nitrite is given during one of the temporary spontaneous elevations which from time to time occur, a fall closely approaching the original is recorded.

The following experiment will serve for purposes of contrast.

Tracing 26*a*.

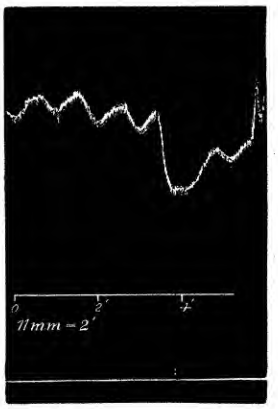
Both splanchnic nerves divided. Inhalation of $\frac{1}{100}$ cub. centim. secondary propyl nitrite.

Tracing 26*b*.



Stimulation of splanchnic, coil 7·5 centims., and simultaneous administration of $\frac{1}{100}$ cub. centim. secondary propyl nitrite.

Tracing 26*c*.



Taken 30 minutes after 26*b*. During occurrences of TRAUBE'S curves administer $\frac{1}{100}$ cub. centim. secondary propyl nitrite.

Experiment.—Cat slightly curarised and steadily etherized. Administration of $\frac{1}{100}$ cub. centim. secondary propyl nitrite. Splanchnics intact. Fall of pressure 44 millims., recovered in two minutes. After splanchnectomy the same administration during a temporary rise of pressure (viz., a rise from 85 to 118 millims.) caused a fall of 39 millims., recovered in 140 seconds (tracing 26*a*). The pressure having fallen again to, and somewhat below, the original level after splanchnectomy, the splanchnic was stimulated by a current (coil 7·5 centims.) just bearable to the tongue (tracing 26*b*), the $\frac{1}{100}$ cub. centim. of secondary propyl nitrites being given at the same time. A rise of pressure of 35 millims. succeeded by a fall of 39 millims. was recorded, as contrasted with 39 millims. from the previous experiment; but the subsequent recovery was more rapid, occurring under the continued splanchnic stimulation—to the normal in 93 seconds—and passing beyond it to 120 millims.

It is worthy of note that the pressure does not fall at once on discontinuing splanchnic stimulation, but outlasts it for 140 seconds and then gradually declines to the previous level. Half an hour subsequent to the administration the pressure had

fallen to 66–7, fluctuation recorded as long waves being present. Secondary propyl nitrite in the original dose (tracing 26*c*) reduced this pressure slowly by 20 millims. The pressure rose in 2 minutes 30 seconds to the normal and passed beyond it.

From a consideration of these curves, it appears—(1) that the constriction of arterioles in the vascular area supplied by the splanchnic may be restored spontaneously and temporarily to some extent, after both nerves have been divided, and then abolished by secondary propyl nitrite.

(2) That the increased pressure resulting from splanchnic stimulation may be reduced by administration of nitrite, but that after recovery of pressure an increased tonus of the vessels may remain for a considerable time.

(3) That when no spontaneous temporary elevation of pressure is present after double splanchnectomy, a reduction of the existing pressure by the nitrite still occurs.

As a corollary to the fact already stated, that such bodies as the secondary propyl, iso-butyl, secondary and tertiary butyl nitrites have proved themselves the most active members of the series of organic nitrites examined in their action upon blood-pressure—the splanchnics being intact—it was found that these prove themselves specially capable of cancelling the rise of pressure which would usually be produced by a given splanchnic stimulation.

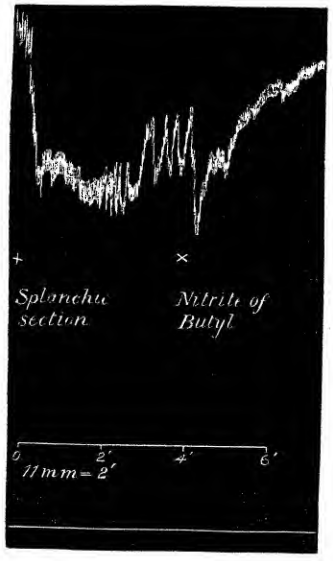
After double splanchnectomy a marked resistance to nitrite effect has been observed during the occurrence of extensive waves of changing pressure, as evidenced by the rapid rise of pressure after the nitrite fall. This effect is indicated by a tracing taken from an experiment in which the splanchnics had just been divided.

At the time shortly before nitrite inhalation the pressure, which was fluctuating between 95 and 82, described four waves having a variation of from 110 to 93 millims. (tracings 27*a* and 27*b*.)

On giving the butyl nitrite $\frac{1}{50}$ cub. centim. the pressure fell from 110 to 79, but 1 minute after commencing, or, in other words, when the summit of the wave which would have followed the other four in regular series was approached, there was a distinct rise. In so short a time as 82 seconds the normal pressure was reached, and thereafter exceeded, the waves gradually disappearing.

	Time.	Pulse.
	secs.	
Before inhalation . . .	..	136
After commencement .	5	140
,, ,, .	25	140
,, ,, .	45	142
,, ,, .	60	142
,, ,, .	85	144
,, ,, .	105	141
,, ,, .	130	139

Tracing 27*a*.

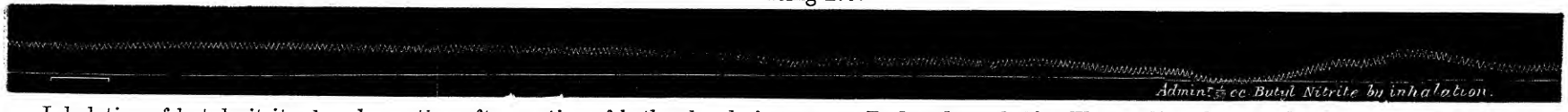


Inhalation of $\frac{1}{50}$ cub. centim. butyl nitrite four minutes after division of splanchnic nerves. The nitrite fall is followed by a rapid rise of pressure. The pulse is shown in 27*b* recorded upon a rapidly moving cylinder.

Tracing 28*a*

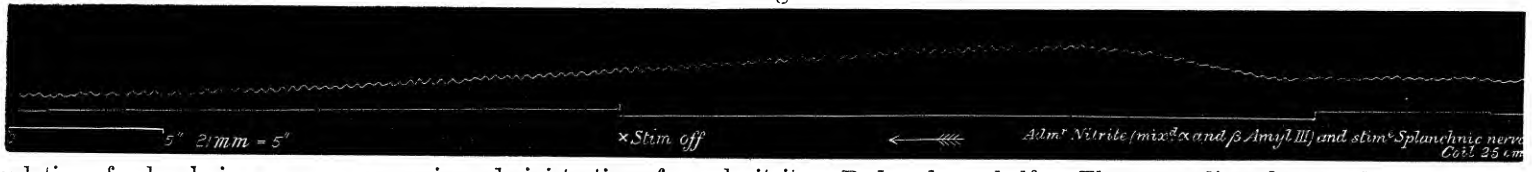
Stimulation of splanchnic nerve (coil 2·5 centims.) and simultaneous inhalation of $\frac{1}{36}$ cub. centim amyl nitrite. For pulse see tracing 28*b*.

Tracing 27*b*.



Inhalation of butyl nitrite $\frac{1}{50}$ cub. centim. after section of both splanchnic nerves. Reduced one-half. The top line shows pulse and pressure, the lower the signal record of the time of administration. See also slow record of pressure, tracing 27*a*.

Tracing 28*b*.



Stimulation of splanchnic nerve accompanying administration of amyl nitrite. Reduced one-half. The upper line shows pulse and pressure, the lower the signal record of administration and stimulation. For course of blood-pressure see slow drum, tracing 28*a*.

Before this administration there appeared to be an unusual vasomotor excitement, which offered some degree of resistance to the nitrite effect.

After dilatation of the vessels had been increased by nitrite, an unusual contraction appears to succeed, as in some of the experiments just recorded. In this instance pressure rises to within 12 millims. of the point at which it stood before splanchnectomy.

It is necessary now to examine somewhat more closely the results of splanchnic stimulation at various periods of nitrite activity. The former may be considered under three headings with regard to the latter. Splanchnic effect occurring—

1. Before inhalation, or during the initial stage of inhalation, anterior to the fall;
2. During the period of fall of pressure; or
3. During a time at which a rise of pressure usually occurs.

If the inhalation of one of the nitrites is made simultaneously with the admission of a strong faradic current to one splanchnic (the companion having been previously divided), a rise of blood-pressure is at once observable. This elevation commences within 3 seconds after the stimulation is begun, and attains its maximum in about 8 to 10 seconds, some variations occurring according to the strength of the current and to the activity of the nitrite given.

Although stimulation is still continued, a distinct and steady fall of pressure commences, the fall at this point coming into contrast with that usually following a simple inhalation, as it shows a nearly equal decline for similar increments of time; whereas after inhalation, as has been already shown, the decline is much greater at first, and thereafter proceeds gradually. The loss of control of the splanchnic is gradual and not sudden. The minimal point of pressure is reached at a time distinctly after that at which it usually occurs, nevertheless a fall to a point below the original pressure level is uniform.

Usual preparation of animal; artificial respiration; both splanchnics divided, the left nerve on electrodes. (Tracings 28*a* and 28*b*.)

Time.	Blood-pressure.	Pulse.	
secs.	millims.		
0	84	168	Before administration splanchnic stimulated coil 2·5, and administered $\frac{1}{36}$ cub. centim. mixed α and β-amyl nitrite
5·5	108	166	
22·5	89	..	Splanchnic stimulation off
26	84	171	
42	62	..	Pressure at lowest and beginning to rise
131	84	..	Pressure normal and rising rapidly
218	95		

This fact is of special significance when it is borne in mind that the powerful closure

of the mesenteric and visceral vessels, which the splanchnic stimulation provokes when administration and stimulation are simultaneous, reduces the free passage of the blood laden with nitrite vapour to the arterioles, and, therefore, must limit the local effect which the drug is capable of producing. It is difficult to see what satisfactory explanation can be given by the advocates of an exclusively central cause of the fall of pressure which occurs during simultaneous nitrite inhalation and splanchnic stimulation, unless they recognise a vascular area more capacious than that dominated by the splanchnic, and beyond its control, which is relaxed by such a central effect. If a less capacious area were relaxed, the splanchnic territory being unimpaired in activity, stimulation of the latter ought clearly to obviate the nitrite fall produced elsewhere.

The initial rise occurring from stimulation of the splanchnic at the same time that nitrite was given is succeeded by a fall, whilst the stimulation is maintained; there is, therefore, an instant during which the original level of blood pressure is crossed as the decline progresses.

This point occurs in from 25 to 30 seconds after the commencement of administration, or, in other words, about the time of greatest nitrite effect for the doses of nitrite used, the splanchnic being unstimulated.

If we imagine all other vascular areas which are usually influenced by nitrite action to be in their condition of maximal dilatation for a given dose at this time, we should expect the usual rapid recovery of pressure to result at this point, if the action of the nitrite were central from the return of activity to the vasomotor centres, but this effect is very rarely witnessed. The pressure is in part falling from a progressive weakening of splanchnic control upon the vessels, to which, as they dilate, more of the nitrite-laden blood has access. In this way a later maximum of dilatation is brought about.

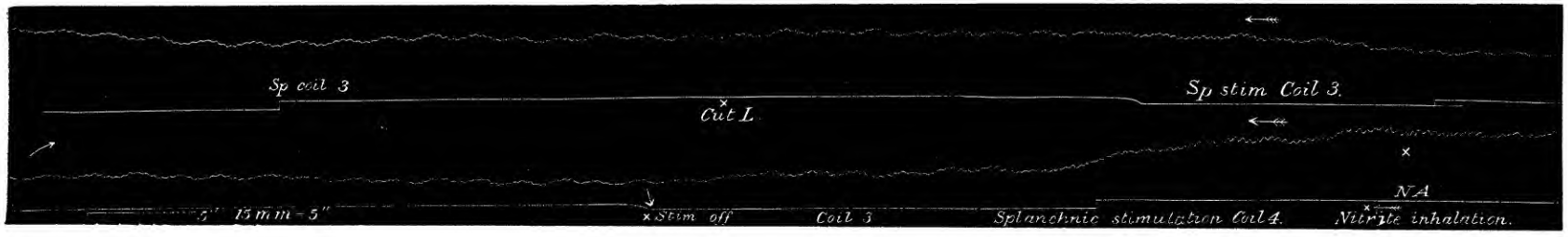
2. If the nitrite administration precedes splanchnic stimulation by such a time interval as admits of the former having caused about half the reduction of pressure of which it is capable (*i.e.*, about 15 seconds after the commencement of inhalation), then the controlling action of the splanchnic is still further reduced, and an immediate rise to the original pressure by stimulation of physiological or somewhat greater strength is not met with, although a slight effect may be produced according to circumstances. How slight this effect actually is may be seen from the following experiment; the fall of pressure was less by 5 millims. than that occurring from the same dose of the same nitrite in the absence of splanchnic stimulation.

Experiment.—Usual preparation. Right splanchnic divided and placed on electrodes. Left splanchnic intact. Artificial respiration. (Tracings 29*a* and 29*b*.)

Tracing 29*a*

Inhalation of $\frac{1}{42}$ cub. centim. amyl nitrite 15 seconds before right splanchnic stimulation. During progress of rise of pressure the other splanchnic nerve is divided, causing arrest of rise. Stimulation of right splanchnic causes great and sustained rise. For pulse see tracing 29*b*.

Tracing 29*b*.



Stimulation of splanchnic nerve following administration of amyl nitrite. Reduced one-half. The lower pair of lines show pulse and the signal record, the upper are continuous with them. For course of blood-pressure see slow cylinder, tracing 29*a*.

Time.	Blood pressure.	Pulse.	
secs.			
0	91	168	
15	76	171	Gave $\frac{1}{42}$ cub. centim. mixed amyl nitrite. (III.)
20	85	174	Splanchnic stimulation coil, 4 centims. and pushed up to 3
36	56		
47	55	..	Lowest pressure
48	..	..	Began to rise
72	76	170	
82	..	..	Stimulation splanchnic coil 3
96	..	..	Stimulation stopped
100	104	170	
120	..	..	Cut left splanchnic
125	96		
140	..	..	Stimulated right splanchnic
148	112	180	

But it may be argued that the stimulation in this case was not continued throughout the nitrite action, and that some controlling effect upon the fall was therefore not recorded. Curves have, however, been frequently obtained in which stimulation was continued fully 1 minute after inhalation commenced, and yet the fall of pressure recorded was within a few millimetres of that obtained in the absence of splanchnic stimulation, although the subsequent rise after the minimum pressure had been reached was rapid.

This effect was especially well marked in the case of iso-butyl nitrite, which, in a given dose, throws the splanchnic more completely out of action than pure nitrite of amyl does.

After the pressure had recovered in these cases the splanchnic was usually tested, in order to ascertain that it still responded; and it was invariably found that a prompt and considerable rise of pressure resulted. It was noticed that late in the course of an experiment, after the pressure had been reduced by double splanchnectomy, and to an additional extent by administering a nitrite, the prolonged depression apt to result could be obviated by stimulating the splanchnic, and that the pressure could even be "pushed up" and retained at a relatively high level by repeating the stimulation at intervals. After nitrite inhalations, succeeding double splanchnectomy, the pressure is frequently seen to rise spontaneously to a higher level than before the administration, and to remain elevated for a considerable time. Whether this is the result of an increased potentiality for contraction of vascular areas after their dilatation is at present difficult to decide, but it seems not improbable that this may be the explanation of the phenomenon.

(3.) Of splanchnic stimulation occurring at the time of commencing recovery of pressure after nitrite action, it is only necessary to say that it markedly accelerates the return of the pressure to, and even beyond, its original level.

VII.—Action of Nitrites upon the Human Subject.

It has been already mentioned that these experiments were confined to obtaining an accurate record of pulse rate, and to noting the various subjective and objective symptoms to which the nitrites give rise.

Inhalation in all cases took place by means of a mask inhaler which was specially constructed by Messrs. Maw, Son, and Thompson.

This consists of a somewhat conical metal box covering the mouth, and fitting accurately over the bridge of the nose by means of a hollow rubber border which could be distended by injection of air. It was provided with three tubes opening out of a common trunk in the front of the mask; one of these had no valve, but the two lateral tubes had each one valve, opening inwards and outwards respectively.

The tube intended for the inspiration of the nitrite had a continuation of india-rubber, in the middle of which a glass bulb was inserted for the reception of the nitrite. Spring clamps were placed on each side of this bulb.

For accurate comparison the results of administering the nitrite to the *same individual*, and usually on the *same day* are contrasted. There is considerable variation in different individuals to nitrite effect. In a distinctly neurotic subject, in whom the prospect of the inhalation alone was apt to cause a marked pulse acceleration, a dose of $\frac{1}{36}$ cub. centim. (= ·023 grm.; NO_2 0·009 grm.) of pure amyl nitrite, increased the rapidity of the pulse (from 77 to 136), the acceleration being accompanied by a very perceptible subjective and objective nitrite effect, but there was afterwards a rapid fall nearly to the normal. In a second subject of a lymphatic tendency the increase of pulse-rate was by no means great, but it was remarkable as being continued much longer than in other subjects of experiment.

The mask having been adjusted to the face, and respiration being regular through the valveless tube, the drum was started at full speed to record the normal pulse-rate,* and the inhalation tube was opened by removing the clamps on each side of the bulb, at the same time that the anterior tube was closed. The time of inhalation was recorded by a signal marker which was under the exclusive care of one assistant, while another assistant watched the face and neck for indications of flushing or other appearances.

Several Aberdeen students kindly gave their assistance in these experiments amongst whom were Messrs. Ettles (who also sketched the apparatus employed), Lendrum, Sutherland, and Taylor.

It is not intended to devote much space to the description of the results obtained, but rather to present them in summarised form.

The nitrites examined were various specimens of: pure α-amyl nitrite; the three mixed α and β-amyl nitrites, designated I., II., and III.; butyl and iso-butyl nitrites; primary and secondary propyl nitrites; and ethyl nitrite.

* The impulse was derived from the cardiac apex, or radial artery, and transmitted to a Marey's recording tambour.

The doses of nitrite employed varied from $\frac{1}{42}$ to $\frac{1}{18}$ cub. centim. Doses of $\frac{1}{18}$ cub. centim. of amyl nitrite caused an acceleration of the pulse, commencing at the end of the first 5 seconds. The acceleration was equivalent to from 65 to 73 per cent. of the pulse rate. Retardation of the pulse during the early stage of administration was not observed. Although the acceleration began between the fifth and tenth seconds, it was from the tenth to the thirtieth that the more rapid increase occurred, the acceleration reaching its maximum somewhat later, viz., at the thirty-fifth second.

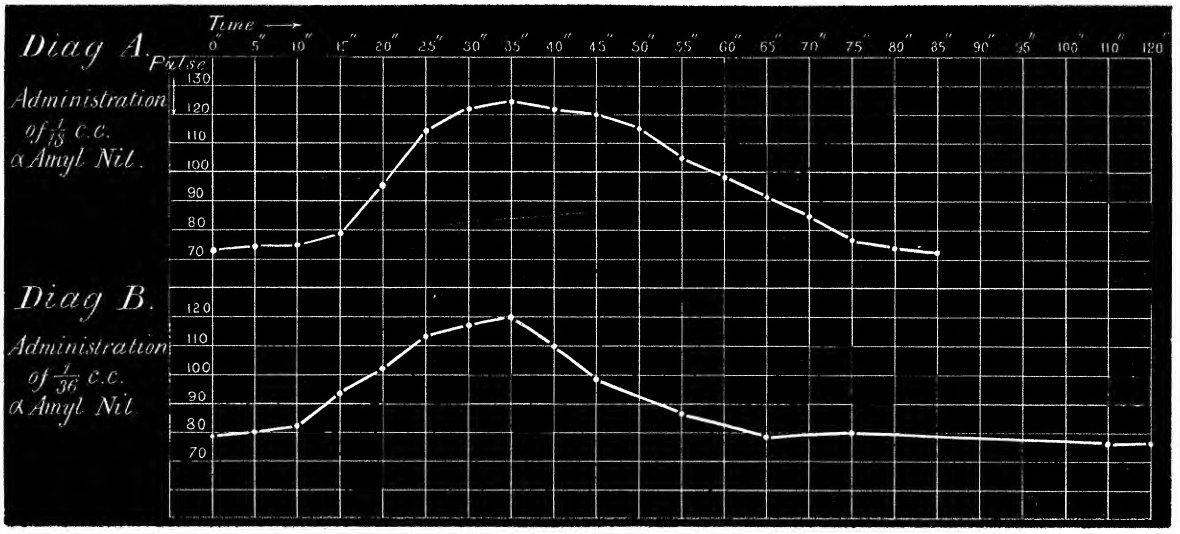
If divided into three periods of 10, 10, and 15 seconds respectively, the percentage of the total acceleration, amounting to 45 to 50 beats, averaged about as follows :—

1st	10 seconds	=	6 per cent.
2nd	10 ,,	=	40 ,,
Last	15 ,,	=	54 ,,

After the maximal acceleration is reached a fall begins somewhat gradually, the pulse returning to its normal within 90 seconds after inhalation commenced. The fall is trivial from the 35th to the 45th second; from the 45th to the 65th second it is most rapid, and then declines more gradually. Fall in successive 10 seconds after maximal acceleration :—

1st	10 seconds	=	10 per cent.
2nd	,,	=	30 ,,
3rd	,,	=	33 ,,
4th	,,	=	27 ,,

Diagrams A and B.



Experiment. Diagram A.—Administration of $\frac{1}{18}$ cub. centim. α-amyl nitrite to T. Ordinates which are united at their summits to form a curve represent intervals of 5 seconds.

T. afterwards stated that the pulsation was violent in his head and carotids; there was slight vertigo. The flushing was very well marked and more lasting than when $\frac{1}{36}$ cub. centim. was given.

	Time.	Pulse.
	secs.	
Pulse before nitrite . .	0	73
Inhalation commenced .	5	74
	10	76
	15	79
	20	95
	25	115
	30	122
	35	125
	40	122
	45	120
	50	116
	55	108
	60	99
	65	91
	70	85
	75	77
	80	73
	85	72

A dose of $\frac{1}{36}$ cub. centim. caused an acceleration of 35 to 40 beats per minute (equal to from 47 to 53 per cent. of the total). The pulse occasionally showed a slight slowing during the second 5 seconds of inhalation; more usually there is acceleration. The maximal acceleration was from 25 to 30 seconds after inhalation commenced, the latter being much the more frequent.

The pulse returned to the normal in from 55 to 60 seconds, and then frequently became distinctly subnormal for a short time.

The relationship of rise and fall may be briefly indicated by the percentage acceleration and reduction of pulse.

secs.	per cent.	
0 to 10	7	Pulse accelerating.
10 „ 20	52	
20 „ 35	41	
35 „ 45	51	Pulse slowing.
45 „ 55	30	
55 „ 65	19	

The figures in these two experiments indicate a later maximal effect, a greater and more prolonged acceleration, and a more gradual decline after the larger than after the smaller dose.

Experiment. Diagram B.—Administration of $\frac{1}{30}$ cub. centim. amyl nitrite.

T. afterwards described his sensations as of active pulsation in head and neck, unaccompanied by dyspnœa. There was no vertigo. The flushing was very well marked, but not of long duration.

	Time.	Pulse.
	secs.	
Pulse before nitrite . .	0	79
Inhalation commenced .	5	80
	10	82
	15	94
	20	103
	25	114
	30	118
	35	120
	40	110
	45	99
	55	87
	65	79
	80	80
	105	75
	120	75

Variations from the Normal α-Amyl Nitrite Effect caused by the Various Organic Nitrites Examined.

The three mixed α- and β-amyl nitrites (I., II., and III.) were administered by inhalation in addition to pure α-amyl nitrite. The action of the four bodies was very similar, that is to say, they caused, for the dose administered, a powerful acceleration of the pulse, and the rate at which the acceleration progressed and receded was nearly the same. If a distinction is justifiable between them, it must be based on a somewhat more powerful action of pure amyl nitrite and the compound I. when compared with II. and III. In the course of three experiments devoted to the comparison of these bodies, and performed on different subjects, it was found that the variation in the pulse-rate in all of them was not greater than four beats per minute for the $\frac{1}{36}$ cub. centim.

The maximal acceleration after doses of $\frac{1}{36}$ cub. centim. is usually from the 28th to the 35th second after the beginning of inhalation, the pulse usually falling to the normal in 60 seconds to 65 seconds. It is usual to witness a temporary subsequent decline in pulse-rate amounting to two beats to three beats below that antecedent to inhalation.

Primary Butyl Nitrite.

In experiments with this compound made on carnivorous animals, the acceleration of the pulse was less marked than in contrast experiments with amyl compounds.

The relationship of the acceleration caused by butyl nitrite to that of amyl nitrite may be represented by percentages taken from three individuals.

T. Butyl nitrite caused an acceleration of 79 per cent. of that produced by α-amyl nitrite.

S. ,, ,, ,, 75 ,, ,, ,,

L. ,, ,, ,, 74 ,, ,, ,,

The maximal acceleration is soon arrived at. It lies between the 25 seconds and 28 seconds after commencing inhalation for the dose of $\frac{1}{36}$ cub. centim.

The return to the normal pulse-rate was usually 3 seconds to 5 seconds earlier than it was after the inhalation of amyl compounds. The subjective symptoms were not so well marked.

Experiment 3, L.—Inhalation of $\frac{1}{36}$ cub. centim. butyl nitrite.

Throbbing in thyroid and carotid regions; pulsation at occiput; felt flushing in face. Afterwards received same amount of mixed amyl nitrite (II.) and flushed more, stating afterwards that he felt pulsation and warmth of surface distinctly greater than during administration of butyl nitrite. The pulse after (II.) showed a greater acceleration.

Iso-Butyl and Secondary Butyl Nitrites.

Both of these bodies cause less acceleration of the pulse than the amyl compounds, but greater than that produced by butyl nitrite. The acceleration occasioned by the secondary butyl nitrite (about 80 per cent. of that produced by α-amyl nitrite) seems to be slightly less than by the iso-butyl compound (about 82 per cent.). The greatest acceleration produced by both of them seems to occur between the 25th and 30th seconds. The subjective symptoms after $\frac{1}{36}$ cub. centim. are further more marked in the case of secondary butyl nitrite; after both of them the characteristic flushing and throbbing are produced by even this small dose.

The duration of pulse acceleration after either of them is shorter by a few seconds than after a corresponding dose (by volume) of α-amyl nitrite.

Primary and Secondary Propyl Nitrite.

Both of these bodies come after butyl nitrite in activity, but of the two, secondary propyl nitrite causes distinctly greater acceleration of the pulse.

For comparison, they may be averaged in doses of $\frac{1}{36}$ cub. centim. with pure α-amyl nitrite, which has the value of cent. per cent.

L. { Primary propyl nitrite 62 per cent.
Secondary ,, 76 ,,

This slight acceleration is early developed and rapidly reduced, a reduction to the normal pulse-rate being reached sooner than with pure amyl nitrite given in an equal dose.

This is specially the case with primary propyl nitrite, which frequently causes an oscillation of pulse-rate, the first acceleration and its rapid reduction being succeeded by a second feeble acceleration.

Ethyl Nitrite.

Given in the most cautious manner, so that the danger of loss is reduced to a minimum, the effects of small doses are almost nil. An ordinary inspiration, or, at most two, volatilizes the whole of such quantities as $\frac{1}{36}$ and $\frac{1}{30}$ cub. centim. A slight feeling of warmth, and a sweetish taste in the mouth are the only sensations.

The acceleration of the pulse is absent or amounts to only two or three beats in 20 seconds after opening the nitrite tube (E. $\frac{1}{36}$ and $\frac{1}{30}$ cub. centim.); the pulse appears to have a distinct tendency to become subnormal after inhalation.

If the $\frac{1}{20}$ cub. centim. be given, an undoubted acceleration of 10, or even 15 beats per minute is recorded, the maximum is from 25 to 30 seconds after administration is begun.

If a decided impression is thus made upon the pulse-rate, a slight acceleration frequently persists for a time, so that it may be 60 to 70 seconds before the reduction to, or below the original rate occurs.

As regards their power of accelerating the pulse, the substances examined may be thus classified, beginning with the strongest :—

(1.) α-Amyl nitrite.
β-Amyl nitrite.
Iso-butyl nitrite.
Secondary butyl nitrite.
Butyl nitrite.
Secondary propyl nitrite.
Primary propyl nitrite.
Ethyl nitrite.

PART II.

VIII.—Action of Nitrites on Striated Muscular Tissue.

Nitrite of amyl is well known to possess a powerful action upon the skeletal muscle of Frogs. Wood pointed out that whether applied in a liquid or concentrated gaseous form a paralysant effect was produced. Brunton speaks of amyl nitrite as a muscle poison in common with all other nitrites. Pick also noticed its paralysant action. As we desired to employ a comparatively simple tissue in further contrast experiments upon the nitrites, and as Frog's muscle seemed to fulfil this condition, we instituted the following inquiry into the direct action of the vapours of nitrites

upon the muscles of *Rana temporaria*. The paralysant action of nitrite is seldom well developed in instances in which the drug has been administered by injection, no doubt from the fact that the heart's activity is apt to be much depressed before there has been sufficient access of nitrite blood to the muscular system to produce a marked effect upon its irritability. All the experiments in this series were made with the triceps (extensor of the leg) and gastrocnemius of *Rana temporaria*. One of the selected pair of muscles was introduced into a muscle chamber which, whilst being absolutely air-tight, admitted of a connection between the muscle and lever for recording purposes. This chamber, which had a capacity of 50 cub. centims., was a modification of the one described by one of us (C.) in vol. 184, 'Phil. Trans.;' it was closed hermetically above by an india-rubber stopper fitting perfectly air-tight; whilst the opening through which the thread passes to the lever was closed below by a little mercury. The thread works without friction. Stimulation is effected by passing a single opening induction shock from the electrode in contact with the femur clamp, to the tendo Achillis, by means of a fine wire attached to the hook inserted into the latter (see fig. 3). The nitrite was introduced by passing the capillary pipette containing it through a small tube luted into the side of the chamber, having a continuation of india-rubber provided with a screw clamp; the introduction of a small fraction of a drop of distilled water into the tube behind the nitrite, as a preliminary, ensured the complete emptying of the nitrite contained in the tube by displacement, on blowing gently through it with a pair of hand bellows. No escape was possible from the chamber; the fact that the characteristic odour of the nitrite was not recognizable in its vicinity, and further that when the cork was removed, frequently after an interval of more than two hours, the odour of the drug was still distinct within the chamber, showed that the precautions for preventing an escape were satisfactory in their operation. The amounts of the nitrites introduced into the chamber varied from $\frac{1}{30}$ to $\frac{1}{400}$ cub. centim. The second muscle for the control experiment was kept at a like temperature under filter paper moistened with normal salt solution.

Although no difference in the reaction of the second muscle owing to the delay in its examination seemed probable, nevertheless in different experiments the order of examination of two contrasted nitrites was reversed, but the results in the two cases were found to be perfectly uniform. A very extensive series of experiments was necessary, as it is impossible to contrast the gastrocnemius of one Frog with that of another without the possibility of introducing error; and so every member of the series had to be contrasted with each of the other members upon the companion gastrocnemii of the same animals. Each experiment was repeated for the sake of certainty at least thrice, and in many cases five or six times. When the effect of the drug in causing passive shortening and rigor was under consideration the nitrite was introduced after the muscle had ceased to extend under the slight axial weight (5 to 20 grms.) with which it was burdened. When the effect upon the work done was to

be considered, a maximal opening stimulation was admitted periodically. The closing stimulation occurring midway between two opening shocks. The closing stimulation was, however, frequently cut out. The speed of rotation of the drums employed was once or four times in an hour.

Fig. 3.

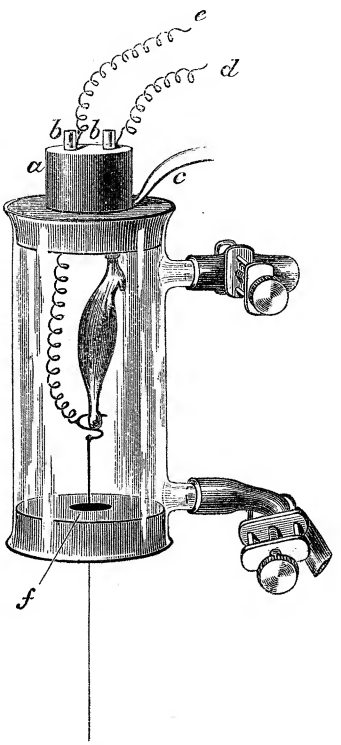


Figure (two-thirds of size) of the air-tight muscle-chamber used in the nitrite experiments.

(The metal band connecting the chamber with the upright as well as the lever are not represented in the sketch.)

The stopper (*a*) which fits air-tight into the opening in the cork at the upper end of the chamber has a double perforation. Both of the openings are closed at their upper ends by glass rods (*b*). The femur is introduced into the lower end of one of these openings and held tightly by a loop of thread, the continuations of which pierce the stopper laterally, so that by traction upon them the bone is clamped in position; these threads are prevented slipping by the pressure of the stopper against the cork rim (*c*). A wire electrode is carried down the side of each glass rod, one of these (*d*) being in connection with the femur round which it is wound, the second (*e*) through the medium of a fine coiled wire with the hook which pierces the tendon. This hook is connected with the lever by a thin silk thread which passes through a fine capillary tube with an hour-glass constriction perforating the bottom of the cylinder. The floor of the cylinder is cupped round the tube so as to afford lodgment to a little mercury (*f*), which renders the chamber perfectly air-tight. The capacity of the closed cylinder was 50 cub. centims.

It is satisfactory to be able to record that the series eventually obtained proved a regular and reliable one with the occurrence of only an insignificant percentage of exceptions, that is to say, if in contrasting the action of nitrites "*a*" and "*b*" on

two companion gastrocnemii, "*a*" was found to have the stronger action; and, if contrasting "*b*" and "*c*," the effect of "*b*" was greater, "*a*" was found almost without exception to be distinctly more active, and stronger than "*c*."

After having examined the action of α-amyl nitrite on striated muscle the consideration was entered upon of other amyl compounds containing a known quantity of β-amyl nitrite in addition to α-amyl nitrite; and, further, of the other alkyl nitrite, which have been discussed with reference to their action upon blood-pressure.

Amyl Nitrite.

It will be seen, when the relative activity of the other nitrites upon muscle is described, that the pure amyl nitrite is one of the weaker members of the series. The effects occasioned by introducing accurately measured quantities of α-amyl nitrite into the air-tight chamber containing a Frog's muscle were as follows :—

The $\frac{1}{100}$ cub. centim. (0·0088 grm.; $NO_2 = 0{\cdot}00346$ grm.) employed in this manner produces a very marked effect, both when the muscle is (*a*) unstimulated, and (*b*) stimulated.

(*a.*) *Unstimulated.*—No effect is observed for the first few minutes, then a faint tendency to contraction, succeeded by a much more distinct and rapid shortening of the muscle, becomes apparent. The shortening, which is due to the gradual passage of the muscle into rigor, continues for a considerable time (often over 2 hours) before its maximum is reached. The higher the temperature of the cylinder the more rapid the effect of the drug; therefore the two companion muscles of the same animal were necessarily examined under as nearly identical conditions of temperature as possible.

The following figures may be taken as illustrative of the action of pure α-amyl nitrite upon muscle :—

Fresh curarized gastrocnemius in air-tight chamber. Temperature 14° C. Admit $\frac{1}{100}$ cub. centim. pure amyl nitrite. Lever multiplies seven times. Weight, 7·5 grms. (axial).

7 minutes 15 seconds. No alteration hitherto, but here commencement of contraction.

Shortening of muscle.	Elevation of lever.
mins.	millims. (lever × 7)
14	9·5
23	15
40	21
60	28·5
120	40
180	47
240	47·5

(This is the limit of rigor caused. The muscle is hard, white, and contracted.)

In another experiment, temperature 14°·5 C., the initial contraction occurs in 10 minutes 40 seconds.

In a third, temperature 15° C., occurs in 6 minutes 5 seconds.

In a fourth, „ „ „ 3 „ 38 „

These figures will give an idea of the possible variations from the same dose, the variations being due partly to temperature, and partly to the receptivity on the part of the muscle. It is found that with companion muscles taken from one animal and subjected to the action of equal quantities of nitrite, at a uniform temperature an almost identical result will be obtained; but if the temperature is higher to which one muscle is exposed, this will determine a more rapid contraction in it, than in the other exposed at a lower temperature. The influence of temperature is not the only cause of variation, however, for when corresponding muscles of two different animals are exposed to equal quantities of nitrite at a uniform temperature, very different results may be obtained. It is evident that there exists a variation in the susceptibility or receptivity of muscles of different Frogs to the effect of the volatile nitrite. The size of muscle did not vary to any appreciable extent, as the Frogs employed in this series of experiments were selected of a nearly uniform weight, varying only from 33 grms. to 35 grms. per individual.

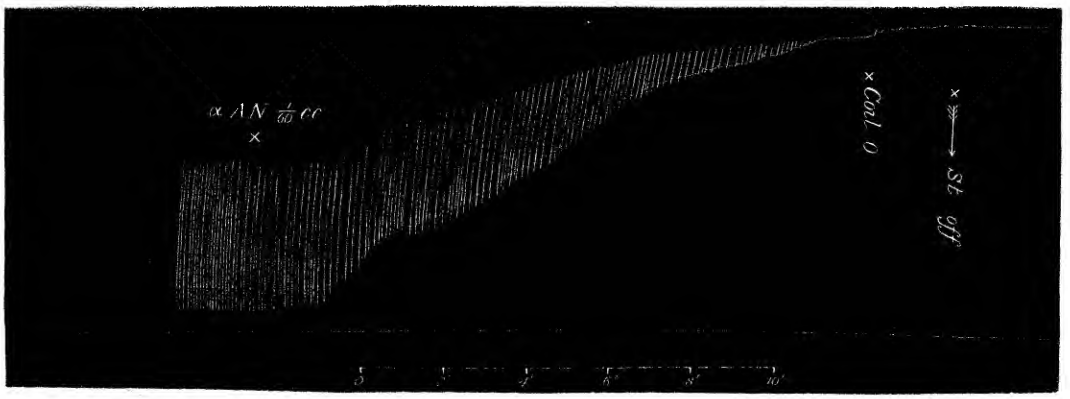
(*b.*) *On Stimulated Muscle.—Effect of α-amyl nitrite* on muscle contracting by periodic stimulation, one opening and one closing maximal shock being administered every 10 seconds weight 7·5 grms. (axial), lever unsupported.

If stimulation has been steadily carried on before the nitrite is admitted, so that the summit of the opening contractions and the basal junction lines are parallel, it will be found that after admission of nitrite, the stimulation being continued, the two lines, if not approximating, continue parallel. No increase of contractile power is observed except that occurring as a result of periodic stimulation of the muscle under an extending weight, nor in cases in which sub-maximal stimulation is used does the contraction become more extensive. Neither is the minimal irritability, as measured by distancing and approximating the secondary from the primary coil, increased by amyl nitrite. After the contractions have remained of equal value for a few minutes after admission of nitrite, or have even diminished a few millims. in extent, the basal line begins to rise, and the value of each contraction to decline slightly. This condition is not maintained steadily till contraction ceases. The basal line usually shows a more or less abrupt rise succeeded by a notch indicative of a partial pause, which strongly reminds one of the notch as seen in the veratria muscle contraction registered upon a rapidly moving surface; this is succeeded by a further rise, and occasionally by a second notch, passing on to the establishment of an irreducible rigor, and the entire cessation of active contraction. This notch is occasionally seen in an unstimulated muscle exposed to nitrite vapour. The experiment from which fig. 30 is taken, may serve to illustrate these points:—

Non-curarized gastrocnemius of *Rana temporaria* axial weight 7·5 grms. One opening and one closing shock in 10 seconds, temperature 14°·5 C., lever × 11, admit $\frac{1}{60}$ cub. centim. pure α-amyl nitrite (= 0·0146 grm.; NO_2 = 0·00576 grm.). Tracing 30.

1 minute active opening contraction	17 millims.	Slight shortening of muscle commencing.	
2 minutes opening contraction.	17 ,,	Shortening of 1 minute.	
4 ,, ,, ,,	14·5 ,,	9 millims.	(first notch.)
6 ,, ,, ,,	11·5 ,,	14·5 ,,	
8 ,, ,, ,,	6·5 ,,	2 ,,	
10 ,, ,, ,,	4 ,,	27·5 ,,	(second notch.)
12 ,, ,, ,,	1·5 ,,	30·5 ,,	
14 ,, ,, ,,	ceased	33 ,,	
16 ,, ,, ,,	,,	35 ,,	

Tracing 30.



Action of α-amyl nitrite on actively contracting muscle. (See protocol.)

The closing stimulation ceases to be steadily operative before distinct shortening of the muscle appears. At a certain stage the action of the nitrite may be suspended, unless a large dose has been employed, and the muscle is rapidly passing into rigor, by emptying the chamber, either by washing out with fresh air or salt solution. It is only, however, during the earliest stages of shortening of a muscle, that a partial restitution of its length and power follows such a proceeding; under a more advanced action of the nitrite, the shortening and the impairment of the active contractions continue. Very small doses of amyl nitrite ($\frac{1}{100}$ cub. centim. = 0·0022 grm.; NO_2 = 0·000865 grm.) tend to weaken and ultimately to abolish active contraction in response to stimulation, without markedly raising the basal line.

Having now recorded the action of pure α-amyl nitrite on striated muscle, the consideration of other amyl compounds containing a known quantity of β-nitrite in addition to the α-nitrite will be made.

In addition to pure amyl nitrite the following were examined :—

Amyl nitrite consisting of			α-nitrite	88·6	per cent.	Marked	II.
			β- ,,	11·4	,, ,,		
,,	,,	,,	α- ,,	84·6	,, ,,	,,	III.
			β- ,,	15·4	,, ,,		
,,	,,	,,	α- ,,	95	,, ,,	,,	I.
			β- ,,	5	,, ,,		

If we contrast the action upon muscles of the first of these (II.) in which a large proportion of β-amyl nitrite occurs with the pure α-amyl nitrite, it is seen that the latter causes a more rapid shortening, and an earlier and more pronounced rigor than the former. The pure α-amyl nitrite causes a more abrupt decline of active contractions when stimulation is made. The mixed nitrite (I.) containing a relatively larger proportion of pure α-amyl nitrite than (II.), was distinctly stronger than (II.), approaching near to the pure α-amyl nitrite in its action.

So far the series is regular, the effect declining with the introduction of β-nitrite; but on examining another nitrite (III.), containing even more (15·4 per cent.) of β-nitrite, it was found that it is more active than (II.), approximating to, though feebler than (I.), in its effect.

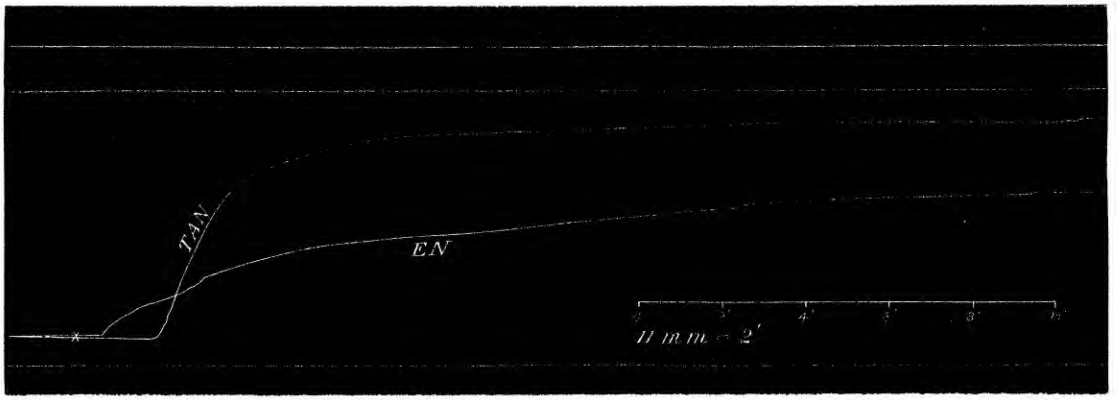
We are not justified, therefore, by taking the series as it stands, in recognising the relative reduction in the proportion of α-nitrite, or the relative increase in the proportion of β-nitrite as the sole cause of diminished action. Up to a certain point the series appears to follow this rule, but the body which, from the fact of its containing the largest amount of β-nitrite, might be expected to prove weakest, turns out stronger in its effect than the body containing somewhat less of β-nitrite. An examination of the relative degree of contraction produced by α-amyl and other bodies of the nitrite series shows the former to be inferior to all the butyl (tracing 33) and propyl compounds, but stronger than ethyl (tracing 46) and methyl nitrites, whilst it is to be regarded as weaker than tertiary, but stronger than secondary amyl nitrite. It is also low in the series when rapidity of production of primary effect is considered. In this respect it is equal with β-amyl nitrite, more active than normal and iso-butyl nitrite, but inferior to the rest of the group.

Tertiary Amyl Nitrite.

The muscular shortening produced by tertiary amyl nitrite is peculiar on account of its relatively rapid appearance and of the speed with which it passes to an approximate maximum. The rise of the lever occasioned is abrupt and extensive. Three bodies of the series of nitrites examined appear to cause an earlier contraction (the amount by volume and the temperature being equal), these are the ethyl

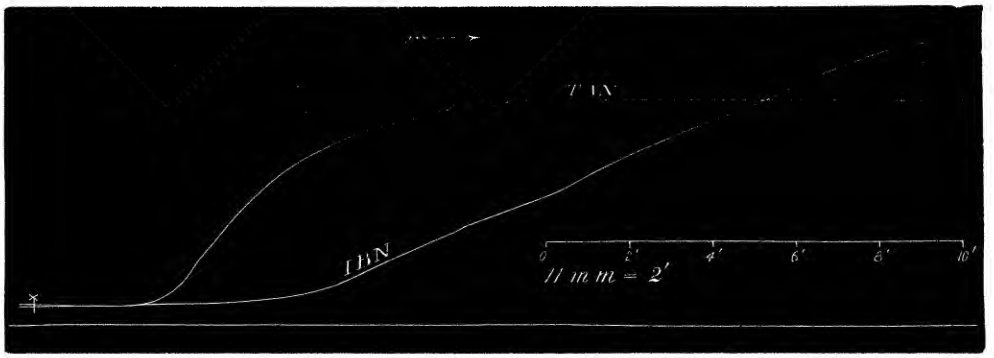
(tracing 32), and methyl, and the secondary propyl compounds. (See tracings 45*a* and *b*, also tracing 43.) As the contraction, when it commences after tertiary amyl, proceeds very rapidly, the extent of the shortening at an early stage is greater than that of iso-butyl nitrite, which, though invariably stronger 30 minutes after applica-

Tracing 31.



Contrasted action of tertiary amyl and ethyl nitrites on resting muscle. (See protocol.)

Tracing 32.



Contrasted action of tertiary amyl and iso-butyl nitrites on resting muscle. (See protocol.)

tion is slower in its first development. The total muscular shortening occasioned by the former, is, however, only distinctly exceeded by the latter, it is very slightly stronger than secondary propyl nitrite (see tracings 43 and 45, *a* and *b*), and the other members of the series succeed it.

In the following table it is contrasted with Iso-butyl Nitrite, Ethyl Nitrite, and Secondary Propyl Nitrite respectively :—

Date.	Nitrite.	Dose.	Weight.	Temperature.	Lever.	Time of first contraction after introduction into muscle chamber.	Extent of shortening of muscle in—						
							5 mins.	10 mins.	15 mins.	18 mins.	25 mins.	30 mins.	60 mins.
			grm.	° C.		secs.	mm.	mm.	mm.	mm.	mm.	mm.	mm.
27.3.90 tracing 31	Tertiary amyl . .	$\frac{1}{100}$ cub. centim. (= ·0089 grm.; NO_2 = ·0035 grm.)	10	10	× 11	138	11·5	25	..	27	27·5		
	Iso-butyl	$\frac{1}{100}$ cub. centim. (= ·0087 grm.; NO_2 = ·0038 grm.)	10	10	× 11	230	·5	·8	..	28	34		
25.3.90 tracing 32	Tertiary amyl . .	$\frac{1}{100}$ cub. centim. (= ·0089 grm.; NO_2 = ·0035 grm.)	10	10·25	× 11	106	22·5	27·5	28				
	Ethyl	$\frac{1}{100}$ cub. centim. (= ·0089 grm.; NO_2 = ·00545 grm.)	10	10·25	× 11	42	11·5	14	17				
25.11.90 tracings 45*a* and 45*b*	Tertiary amyl . .	$\frac{1}{200}$ cub. centim. (= ·00445 grm.; NO_2 = ·0035 grm.)	20	12·5	× 9	116	25	34	36·5	37	37·25	37·25	46
	Secondary propyl .	$\frac{1}{200}$ cub. centim. (= ·00435 grm.; NO_2 = ·00224 grm.)	20	12·5	× 9	78	8	20·5	24·25	32	33	34·25	40

The Butyl Compounds.

Of these the following have been examined :—

1. Primary butyl nitrite.
2. Iso-butyl nitrite.
3. Secondary butyl nitrite.
4. Tertiary butyl nitrite.

The action of members of this group, with one exception, is distinguished by its strength. Passive contraction of the muscle, followed by a well-marked rigor, occurs when a very dilute atmosphere of the nitrite is admitted to the muscle. Even so small an addition as the $\frac{1}{300}$ cub. centim. of some of these bodies may cause a distinct rigor.

This fact will of course suggest an early modification in active contraction resulting from stimulation. Active contraction is in fact rapidly abolished when the dose of nitrite is sufficient to develop rigor, and more slowly when the dose is too small to induce this condition.

In order of activity as regards strength of action on muscle, they take the following order :—

(1.) Iso-butyl nitrite.
(2.) Secondary butyl nitrite.
(3.) Tertiary butyl nitrite.
(4.) Normal butyl nitrite.

In speed of action they are placed thus :—

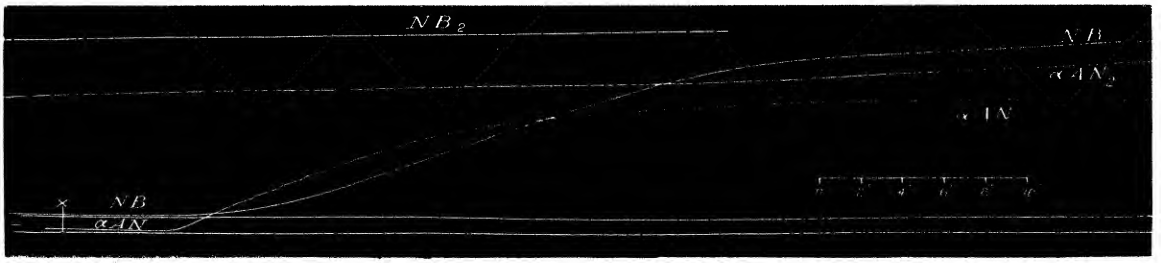
(1.) Tertiary butyl nitrite.
(2.) Secondary butyl nitrite.
(3 and 4.) Butyl and iso-butyl nitrites.

In the latter respect, though the tertiary is slightly earlier in its action than the secondary, the difference is by no means marked. The butyl and iso-butyl nitrites are so similar that it would not be warrantable to separate them.

Normal Butyl Nitrite.—This substance is the weakest of the butyl series as regards the extent of shortening it produces, and it even stands low in this respect in the general series. Thus it is to be placed after both iso-propyl and normal propyl, and secondary and tertiary butyl nitrite, although it is stronger than α-amyl nitrite and than ethyl and methyl nitrites.

In speed of action it is one of the latest; α-amyl nitrite produces shortening before it, whilst ethyl and methyl nitrites, the propyl and the other butyl compounds, with the exception of iso-butyl nitrite, which is about equal, are all more active.

Tracing 33.



Contracted action of butyl and α-amyl nitrites on resting muscle. (See protocol.)

When the rise of the basal line commences it is comparatively slow in reaching its maximum.

($\frac{1}{100}$ cub. centim. = 0·0088 grm.; NO_2 = 0·00393 grm.)

The following experiments will illustrate the relative effect of this nitrite compared with that of α-Amyl Nitrite and Secondary Propyl Nitrite respectively.

Date.	Nitrite.	Dose.	Temperature.	Weight. (lever.)	Length. (lever.)	Time of first contraction after introduction into muscle chamber.	Extent of shortening of muscle in—						
							5 mins.	10 mins.	15 mins.	20 mins.	25 mins.	30 mins.	60 mins.
			° C.	grms.		secs.	mm.	mm.	mm.	mm.	mm.	mm.	mm.
13.11.90 tracing 33	Butyl	$\frac{1}{100}$ cub. centim. (= ·0088 grm.; NO_2 = ·000393 grm.)	11	20	× 9	327	..	3	10·5	21	29·5	37	46·5
	α-Amyl	$\frac{1}{100}$ cub. centim. . . .	11	20	× 9	218	1	11	21	28	31	33	35
13.11.90	Butyl	$\frac{1}{200}$ cub. centim. (= ·0044 grm.; NO_2 = ·001965 grm.)	11·5	20	× 9	345	..	2	4·5	6	6·25	7	10·5
	Secondary propyl.	$\frac{1}{200}$ cub. centim. (= ·00435 grm.; NO_2 = ·0019 grm.)	11·5	20	× 9	180	1	3	5·5	7·5	10·5	12	15·5

Iso-butyl Nitrite.—This nitrite is interesting as being the most active substance in the series when judged by the extent of shortening which is produced, 30 minutes to 60 minutes, or at any subsequent time after its introduction into the muscle chamber; whilst it is almost at the other end of the series when the speed of the initial shortening is measured. In the former respect it is approached most nearly by tertiary amyl nitrite and secondary butyl nitrite; whilst in the latter it stands with normal butyl nitrite slightly below α-amyl nitrite.

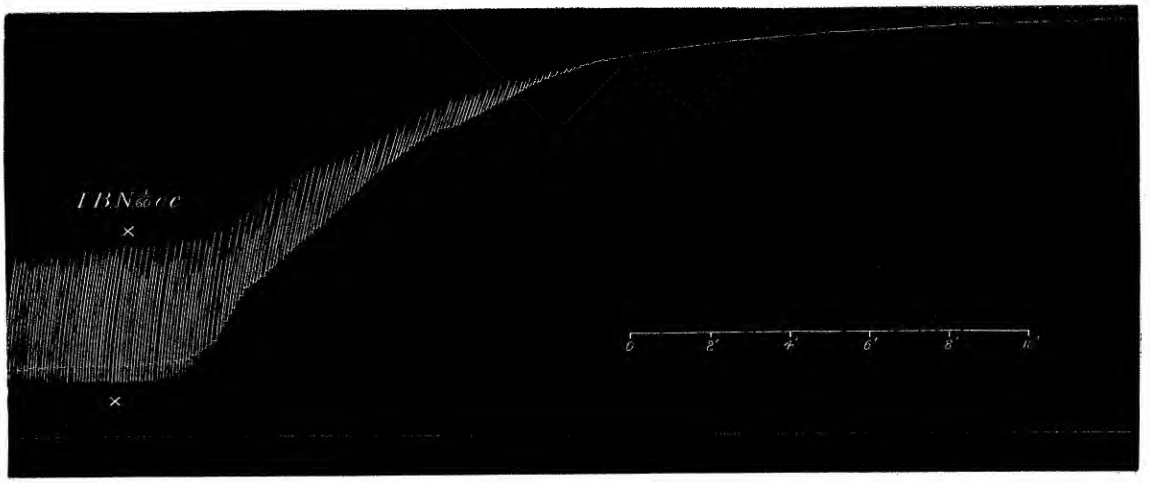
Even such a small dose as the $\frac{1}{350}$ cub. centim. ($\doteq$ 0·00248 grm.; NO_2 = 0·001 grm.) is capable of causing a decided effect, as the following figures will demonstrate:—

Iso-butyl nitrite, $\frac{1}{350}$ cub. centim., introduced into the air-tight muscle-chamber, in which a gastrocnemius is contracting in response to maximal stimulation—(one opening and one closing stimulation every 10 seconds).

LEVER × 7. Weight 7·5 grms. (axial). Temperature 9°·5 C.

Time.	Maximal contraction (opening).	Elevation from abscissæ.
mins.	millims.	millims.
0	12	0
4	12	0
8	12	0
10	11·5	·75
14	11	2·5
18	9·5	5
22	7	10
26	5·5	11
30	2	12
34	0	13

Tracing 34.



Action of iso-butyl nitrite on contracting muscle.

The effect of a large dose upon an actively contracting muscle is well demonstrated by the following notes (tracing 34):—

Iso-butyl nitrite, $\frac{1}{60}$ cub. centim. (= 0·0145 grm.; NO_2 = 0·00633 grm.). Temperature 14° C. Gastrocnemius (non-curarized) in muscle-chamber.

LEVER × 11. Weight 7·5 grm. (axial). Stimulation as before.

Time.	Maximal contraction.	Elevation from abscissæ.
mins.	millims.	millims.
0	16·5	0
2	16·5	1·25
4	11	13
6	5	23
8	4·5	32
10	2	37
12	·5	40·5
14	0	42
16	0	43
18	0	43·5
20	0	44

The muscle was in white rigor. This tracing may be contrasted with tracing 30 in which α-amyl nitrite was applied to the companion muscle under exactly similar conditions.

It will thus be seen that in an air-tight chamber whilst extremely small quantities of iso-butyl nitrite vapour produce a marked effect upon active and passive contraction of striated muscle, in larger amounts the effect becomes a very powerful one.

The basal curve of active contraction is peculiar, as many of those caused by the nitrites are, in showing when the record is made upon a slowly moving surface, two notches in its ascent, which bring to mind the summation of stimulations in a muscle exposed to induction shocks delivered rapidly, and even more to the peculiar summated appearance observable at the commencement of contraction of the veratrine muscle, when its contraction is recorded on a rapidly moving surface.

A contrasted experiment between iso-butyl nitrite and ethyl nitrites, in which no stimulation was made, may be shortly mentioned here. (Tracing 35.)

Tracing 35.

Contrasted action of iso-butyl and ethyl nitrites upon resting muscle. (See protocol.)

Amount.	Weight.	Temperature.	Lever.	Time of first contraction after introduction into muscle-chamber.	Extent of shortening of muscle in		
					5 mins.	10 mins.	20 mins.
	grms.	° F.		secs.	mm.	mm.	mm.
17.3.90.							
Iso-butyl nitrite, $\frac{1}{100}$ cub. centim. (= 0·0087 grm.; NO_2 = 0·0038 grm.)	7·5	54	×6	196	2·5	14·5	25
Ethyl nitrite, $\frac{1}{100}$ cub. centim. (= 0·0089 grm.; NO_2 = 0·00545 grm.)	7·5	54	×6	76	6	9·5	14

Although in this experiment the reaction of the muscle is not vigorous, the relationship between the two nitrites as to speed and extent of contraction occasioned is preserved. (See also tracings 36, 38, 44, and 48.)

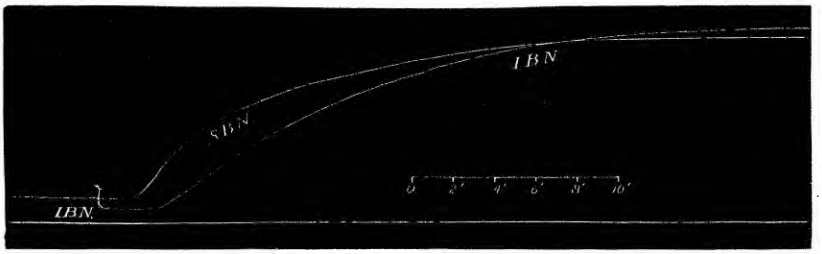
Secondary Butyl Nitrite.—In strength of effect this compound comes after iso-butyl and tertiary amyl nitrites; it is near to secondary propyl nitrite, than which it is slightly stronger. It does not cause the abrupt rise of the lever which the tertiary compound produces.

In speed of action it appears to be after the propyl nitrites, and slightly after tertiary butyl nitrite; it is therefore a long way behind the methyl and ethyl compounds in this respect.

The α-amyl nitrite and both iso-butyl and normal butyl nitrites are slower in their action.

The following experiment will serve to contrast the effect of iso-butyl and secondary butyl nitrites upon the resting muscle.

Tracing 36.



Contrasted action of secondary butyl and iso-butyl nitrites on resting muscle. (See protocol.)

Companion gastrocnemii of frog of 27 grms. Weighted with 7·5 grm. (axial.) Lever × 11. Temperature, 11°·5 C. (Tracing 36.)

To No. 1 admit $\frac{1}{200}$ cub. centim. iso-butyl nitrite.
„ 2 „ „ secondary „

Time.	Shortening.	
	1	2
secs.		
82	..	commenced
120	commenced	
240	4 millims.	13 millims.
480	17·5 „	26 „
960	36·5 „	37 „
1440	45 „	42 „
1920	47·5 „	42·5 „

The activity of secondary butyl nitrite with reference to muscle runs very parallel with that of the secondary propyl compound (see tracing 37, *a* and *b*). The latter, however, whilst occasioning a somewhat more rapid occurrence of passive contraction does not produce the same degree of shortening of the muscle after 30 minutes' application, nor does it so rapidly abolish active contraction, if this is in progress from stimulation. If, during the early elevation of the basal line from the effect of secondary butyl or other nitrites, the muscle which has been stimulated periodically is allowed to rest for a short time, it will be observed that relaxation takes place, the lever sinking to a position distinctly below that of the basal line at the time the active contraction ceased. The first active contraction when stimulation is resumed is an extensive one, but thereafter the basal line rises in sequence to its former course. This result can be obtained steadily, though in progressively diminishing extent, so long as the muscle contracts actively, but after it has ceased to respond to stimulation relaxation is no longer witnessed, excepting some hours later, when, if a heavy weight and a comparatively small amount of nitrite has been employed, some relaxation may occasionally be witnessed. In the early stages of its action the shortening of the muscle is in excess

of the rigor produced, and the difference between the two is attributable to a retardation in relaxation after active contraction, which occasions a temporary shortening, when stimulation recurs with sufficient rapidity. The following experiment, whilst serving to contrast the secondary butyl and propyl nitrites, will also show the result of a pause in the course of stimulation.

The two gastrocnemii of a frog of 26 grms. are exposed in succession to the $\frac{1}{200}$ cub. centim. of secondary butyl (1) and secondary propyl nitrites (2) respectively, after maximal stimulation (one opening shock every 4 seconds, the closing shock being cut out) had been admitted for 3 minutes (tracing 37, *a* and *b*).

Weight 20 grms. (axial). Lever × 9. Temperature 8°·5 C. Tracing 37, *a* and *b*.

	Time.	(1.)		(2.)	
		Active contraction.	Basal line shortening.	Active contraction.	Basal line shortening.
	secs.	millims.	millims.	millims.	millims.
	..	22	0	23·5	0
Introduce nitrites . .	0				
	32	..	..	24	commences
	50	22·5	commences		
	240	20·5	10·5	20·5	12·5
	480	7·5	26	14	26
	720	4·5	30·5	8·5	29
	960	·5	31	2·5	27·5
	1070	ceased			
	1200	..	..	ceased	27

Secondary propyl nitrite shows a somewhat earlier shortening, a less extensive rigor, and a later abolition of active contraction. The difference between these two nitrites is, however, never an extensive one.

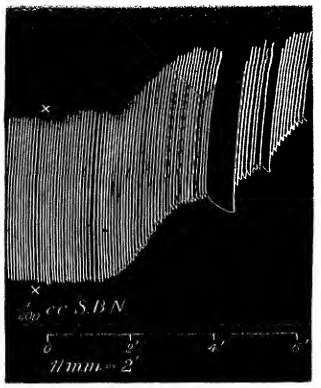
Tertiary Butyl Nitrite.—The curve of passive contraction of the tertiary butyl compound is peculiar and distinctive, the action of the drug producing a passive contraction of muscle which proceeds with great rapidity. In one experiment, $\frac{1}{100}$ cub. centim. was introduced into a chamber containing a resting muscle. Shortening commenced in 2 minutes 30 seconds, and the muscle passed with great rapidity into further contraction and rigor, so that in 5 minutes a degree of contraction was reached which did not markedly increase for over 30 minutes afterwards. The total shortening effect is small when compared with that of iso-butyl nitrite, but it is sooner developed, the maximum being relatively much more rapidly attained.

The contraction produced by iso-butyl nitrite is relatively slower in appearing, the ascent of the curve is more gradual, but it is continuous until a distinctly higher level is reached than in the case of the tertiary compound. Response to stimulation ceases sooner in the case of the former.

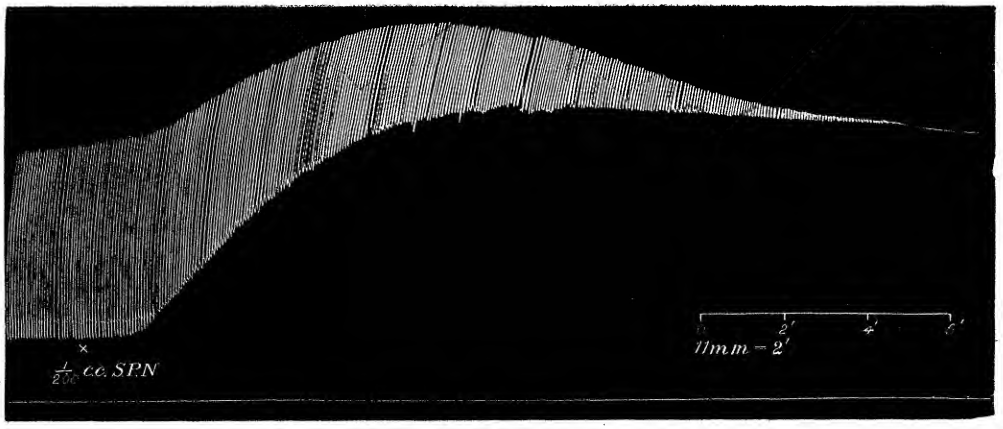
The following experiments serve to contrast the effects of iso-butyl nitrite and

tertiary butyl nitrite. The extent of the action of the former in contrast with the latter is somewhat excessive, but the contraction is highly characteristic in each instance.

Tracing 37*a*.



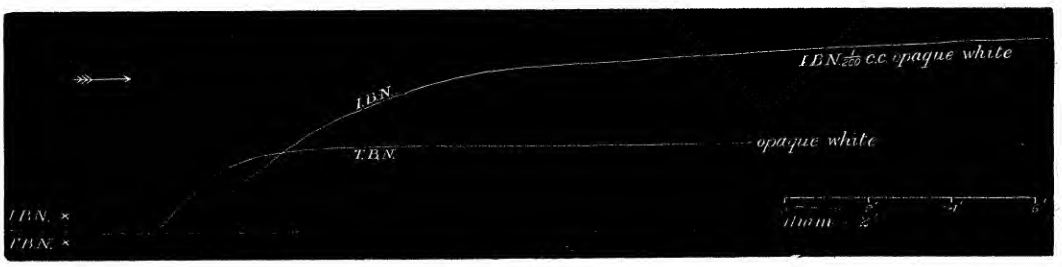
Tracing 37*b*.



Contrasted action of secondary butyl and secondary propyl nitrites upon actively contracting muscle. Stimulation is twice interrupted in the case of the former. (See protocol.)

Experiment.—Contrasted action of two companion muscles placed successively in an air-tight chamber (gastrocnemius of *Rana temporaria*) 10°·5 C. Weight 7·5 grms. (axial). Lever × 7. No stimulation. (Tracing 38.)

Tracing 38.



Contrasted action of tertiary butyl and iso-butyl nitrites upon resting muscle. (See protocol.)

	Time.	Passive contraction.		Passive contraction.
	secs.	millims.		millims.
Admit $\frac{1}{200}$ cub. centim. (= 0·0435 grm.; NO_2 = 0·0019 grm.) iso-butyl nitrite	0	..	Admit $\frac{1}{200}$ cub. centim. (= 0·0043 grm.; NO_2 = 0·00189 grm.) tertiary butyl nitrite	
	229			begins
	316	begins		
	420	5		15·5
	660	24·5		21·5 (curves cross here)
	900	32		22
	1140	39		22
	1380	41		22·5
	1620	42·5		22·5
	1860	43·5		22·5

Both the muscles, but especially that exposed to iso-butyl nitrite, were in a state of opaque white rigor.

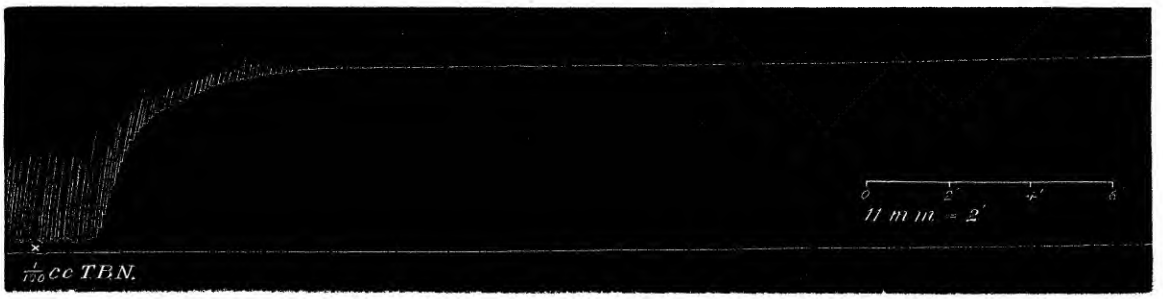
(25.7.90.) Tertiary butyl nitrite, when admitted to an air-tight muscle-chamber in which a muscle is periodically contracting, causes the basal line to rise rapidly, and soon abolishes response to stimulation. Gastrocnemius of frog in air-tight chamber one opening and one closing maximal stimulation every 10 seconds. Lever × 7. Weight 10 grms. (axial). Temperature 15°·3 C. Opening contraction 14·5 millims. (Tracing 39.)

	Time.	Passive shortening.	Active contraction.
	secs.	millims.	millims.
Admit $\frac{1}{100}$ cub. centim. (= 0·0086 grm.; NO_2 = 0·00378 grm.). Tertiary butyl nitrite	0		
	109	Shortening commences	13·5
	120	2	13·5
	240	22	3·5
	480	28	1
	720	28·5	Ceased
	960	28·5	
	2160	28·75 Muscle in white rigor	

The position of tertiary butyl nitrite in the series, as regards the shortening of muscular tissue it ultimately produces, appears to be above normal butyl nitrite, whilst it is inferior to both the other butyl compounds, to tertiary amyl and to secondary propyl nitrite. With reference to the length of time elapsing between the introduction of nitrite and the first evidence of passive contraction, it stands below

the propyl compounds and above normal butyl nitrite. The rapid development of passive muscular contraction it occasions is most closely approached by tertiary amyl nitrite.

Tracing 39.



Action of tertiary butyl nitrite on actively contracting muscle. (See protocol.)

Contrasting the butyl series with the amyl nitrites it may be stated, in general terms, that the former are distinctly more vigorous in their action, in so far as the shortening produced in striated muscular tissue is considered; an exception must, however, be made in the case of tertiary amyl nitrite, which exceeds all the butyl compounds in this respect, excepting the iso-butyl nitrite. Butyl and iso-butyl nitrites give rise to a shortening which has its first appearance after that produced by α-amyl and α- with β-amyl nitrites. The secondary and tertiary butyl nitrites are more rapid, but less so than tertiary amyl nitrite.

The Propyl Nitrites.

The primary propyl and secondary propyl compounds were examined. Of these two bodies, propyl nitrite is the weaker in its total effect upon muscle shortening. It is, however, rapid in action, so that in this respect it stands, with the exception of tertiary amyl and secondary propyl nitrite, the ethyl and methyl compounds, at the head of the list.

Contrasted with the other nitrites enumerated below, the same volume of each of these and of propyl nitrite being employed in each experiment, the results are as follows:—

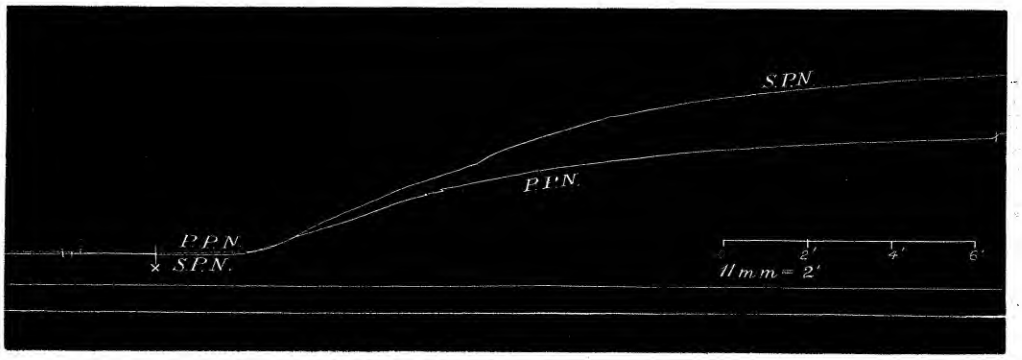
Ethyl nitrite causes an earlier contraction, but propyl nitrite a greater shortening.

Tracing 40.

Action of primary propyl nitrite on resting muscle. The curve of ethyl nitrite is not given. (See protocol.)

Secondary propyl nitrite acts very slightly sooner, and is distinctly stronger than the primary compound.

Tracing 41.



Contrasted action of primary and secondary propyl nitrites on resting muscle. (See protocol.)

α-Amyl nitrite causes a later contraction and a weaker shortening effect.

Tertiary amyl nitrite is slightly more rapid in causing shortening, and produces more powerful shortening.

A few figures will give a general indication of the difference of reaction. All are taken from the gastrocnemius excepting the last, which is from the triceps.

Nitrite.	Dose.	Temperature.	Weight.	Lever.	Initial shortening.	Passive shortening in—		
						15 mins.	30 mins.	60 mins.
	cub. centim.	° C.	grm.		secs.	mm.	mm.	mm.
Propyl* . . .	$\frac{1}{100}$	7·75	10	× 9	240	10	19·5	Much stronger.
Ethyl					130	13	19	
(tracing 40)								
Primary propyl .	$\frac{1}{200}$	12·5	20	× 9	82	22	..	27
Secondary propyl					77	14·5	..	38
(tracing 41)								
Propyl	$\frac{1}{200}$	14·5	10	× 9	109	22·5	23	31·5
α-Amyl					185	15·5	17	24
Propyl	$\frac{1}{200}$	12·6	10	× 11	240	24	34	
Tertiary amyl .					189	34	37	

The action of primary propyl nitrite upon a contracting muscle is well illustrated by the following experiment. (Tracing 42.)

An opening stimulation was delivered to the gastrocnemius every 4 seconds. Temperature, 16° C. Weight, 7·5 grms. (axial). Lever × 7.

* Both the muscles in this experiment yielded a passive shortening with a notch. This is interesting, as though seldom witnessed in absence of stimulation, it is very frequent during its occurrence.

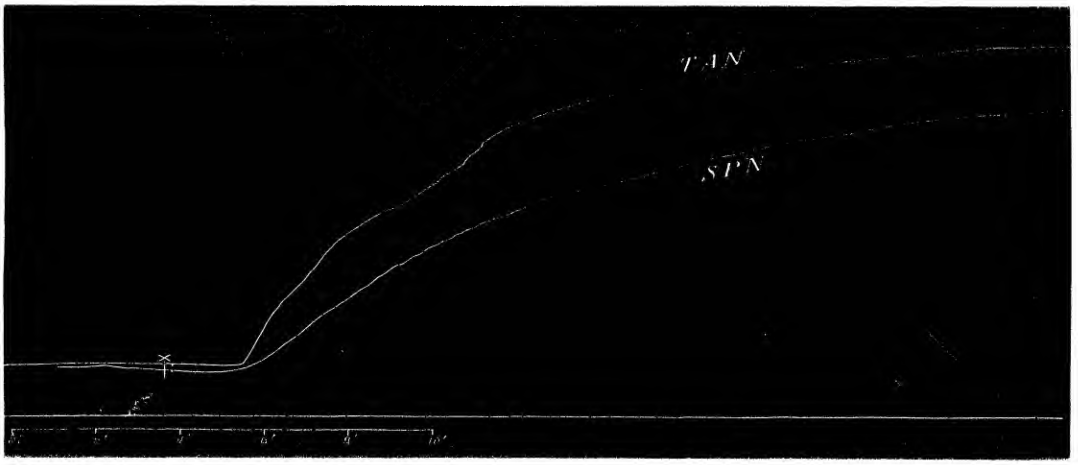
	Time.	Passive shortening.	Active contraction.
	secs.	millims.	millims.
Admit $\frac{1}{250}$ cub. centim. primary propyl nitrite. (= 0·0018 grm.; NO_2 = 0·00061 grm.).	0	..	16·5
	98	Commences	16·5
	240	4	16
	480	12·5	11
	720	16	5·5
	960	18	1·75
	1200	19	Ceased.

Tracing 42.

Action of primary propyl nitrite on actively contracting muscle. (See protocol.)

Two distinct periods of arrest of passive shortening of the muscle will be observed in this curve, one being within 1 minute of commencing contraction, the second 3 minutes later.

Tracing 43.



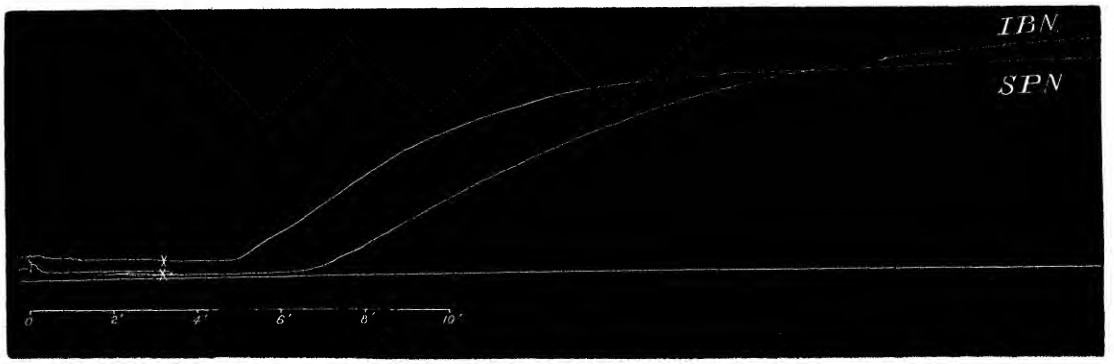
Contrasted action of secondary propyl and tertiary amyl nitrites on resting muscle. (See protocol.)

Secondary Propyl Nitrite.—This is a more active body than propyl nitrite, it is not far behind secondary butyl nitrite (tracing 37α) and tertiary amyl nitrite in the

extent of the contraction it occasions. It produces its initial effect also with rapidity, though it is much behind methyl and ethyl nitrites. In this respect it stands near to tertiary amyl and primary propyl nitrite. The passive muscular contraction does not pass on to an approximate maximum nearly so rapidly as after the exposure of a muscle to an equal dose of tertiary amyl or tertiary butyl nitrite.

The following figures will serve to show the relative difference in reaction of muscles to iso-butyl and other nitrites.

Tracing 44.



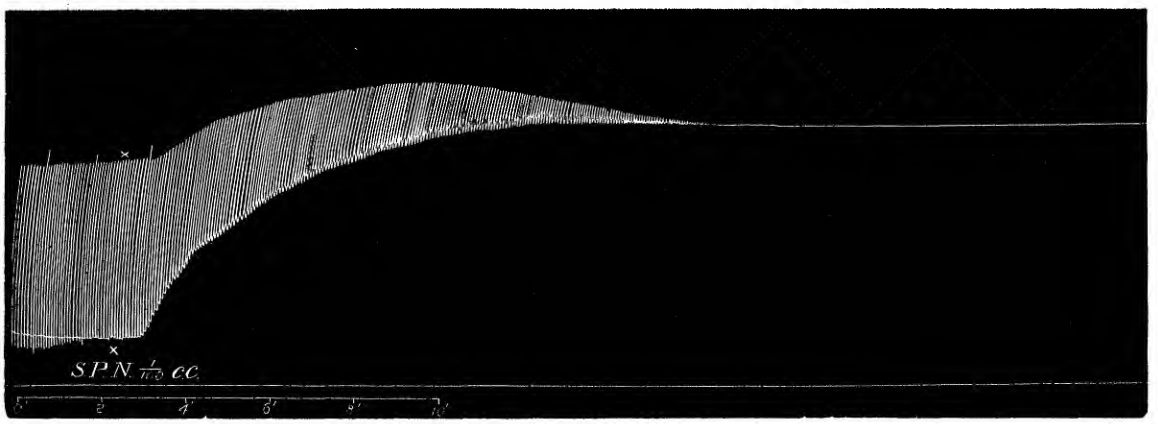
Contrasted action of secondary propyl and iso-butyl nitrites on resting muscle. (See protocol.)

Nitrite.	Dose.	Temperature.	Weight.	Lever.	Initial shortening.	Passive shortening in—			
						15 mins.	30 mins.	45 mins.	60 mins.
	cub. centim.	° C.	grms.		secs.	mm.	mm.	mm.	mm.
Secondary propyl / Secondary butyl	$\frac{1}{100}$	12	2·20	× 9	65	22·5	24·5		
					95	24·5	27·5		
Secondary propyl / Tertiary amyl . (tracing 43.)	$\frac{1}{100}$	9·5	20	× 9	92	32	38		
					109	39·5	43·5		
Secondary propyl / Iso-butyl . . . (tracing 44.)	$\frac{1}{200}$	11·5	20	× 9	114	24	32		
					202	25	26		

On contracting muscle, secondary propyl nitrite is powerfully active. It abolishes active contraction rapidly though less so than equal volume of secondary butyl nitrite, which is therefore to be classified as slightly stronger. The experiment (tracing 37*a*) must be referred to and contrasted with tracing 37*b* secondary propyl nitrite taken from the companion muscle. The passive shortening of the latter is rather less whilst the abolition of active contraction is relatively later. These points are still more clear when tertiary amyl and iso-butyl are contrasted with the secondary propyl nitrite. We shall only introduce one example of an experiment in which this contrast was made.

(12.2.90. Tracing 45, *a* and *b*.) Gastrocnemii of small frog of 20 grms. Stimulation by one (opening) induction shock every 4 seconds. To one muscle, $\frac{1}{100}$ cub. centim. tertiary amyl nitrite (tracing 45*a*) was conveyed in the air-tight chamber, to the other $\frac{1}{100}$ cub. centim. secondary propyl nitrite (tracing 45*b*). Weight, 20 grms. Lever × 9. Temperature, 8°·5 C.

Tracing 45*a*.



Action of secondary propyl nitrite upon actively contracting muscle. Contrast with tracing 45*b*. (See protocol.)

Tracing 45*b*.

Action of tertiary amyl nitrite upon actively contracting muscle. Contrast with tracing 45*a*. (See protocol.)

Time.	Secondary propyl nitrite.		Tertiary amyl nitrite.	
	Basal line elevation.	Active contraction in—	Basal line elevation.	Active contraction in—
secs.	millims.	millims.		millims.
0	0	24	0	26
50	Commenced	..	Commenced	
65				
120	10·5	16·5	9	18
240	19	13·5	24	8·5
480	26·5	8	32	3·5
660	..	..	..	Ceased
720	28	1·75	31	
880	..	Ceased		
960	27·5	..	31·5	
1200	27·5	..	31·5	
1440	28			

The result of this experiment is, in all respects, characteristic of the difference between the two nitrites examined. Tertiary amyl nitrite causes shortening slightly later, but this proceeds more rapidly when it is established, it also abolishes active contraction more speedily than secondary propyl nitrite does.

Ethyl Nitrite.—On account of its low boiling-point (17° C.), and the consequent danger of loss by evaporation, this substance has to be handled with great care. The temperature of the measuring pipette and bottle must be kept down by immersion in ice. By adopting such and other precautions, which a little experience in working with this substance showed to be necessary, the experiments were, it is believed, made free from error.

The initial passive contraction of a muscle exposed to vapour of ethyl nitrite is rapid in making its appearance, more so than all other members of the series examined, with the exception of methyl nitrite.

Extent of dose introduced, temperature under which the experiment is conducted, etc., produce modification in speed of action, as in the case of all other nitrites.

Unless the dose of ethyl nitrite administered is large, the total shortening of the muscle which such an amount is capable of causing is only gradually produced, and in this respect ethyl differs from tertiary butyl and tertiary amyl nitrites, which occasion a rapid shortening of the muscle approximating to the maximal effect realizable from such small doses. With large doses of ethyl nitrite an approximate maximum is rapidly produced. If stimulation is admitted, the individual contractions rapidly decline in extent as the basal line rises, and in a few minutes these are suspended altogether.

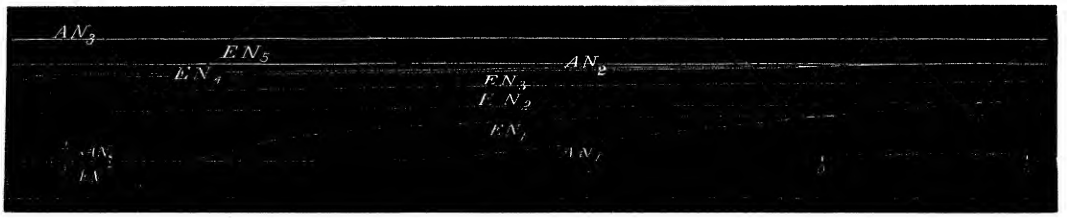
The following figures will indicate the course of an experiment :—

Two (companion) gastrocnemii were subjected to the action of amyl nitrite and ethyl nitrite respectively.

The original basal line of the two is coincident.

(14.3.90.) *Experiment.* 15 minutes drum; 32 millims. = 2 minutes.—Gastrocnemius of frog. Lever × 11. Weight 10 grms. (axial). Temperature 14° C. Tracing 46.

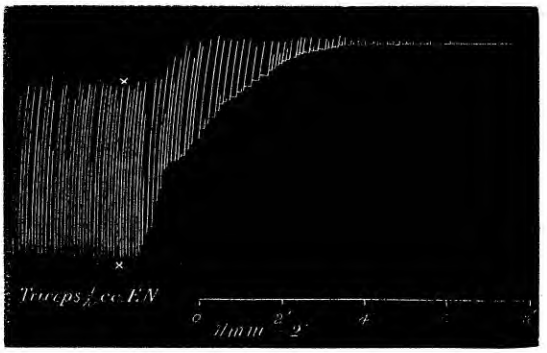
Tracing 46.



Contrasted action of ethyl and amyl nitrite on resting muscle. (See protocol.)

Time.	Ethyl Nitrite.	α-Amyl Nitrite.
secs.		
0	Admit $\frac{1}{50}$ cub. centim. (= 0·00178 grm.; NO_2 = 0·0109 grm.)	Admit $\frac{1}{50}$ cub. centim. (= 0·0176 grm.; NO_2 = 0·0076 grm. α-amyl nitrite)
41	Contraction commences	
120	6·5 millims.	
150	..	Contraction commences
240	9·5 ,,	2 millims.
480	10 ,,	12 ,,
900	12 ,,	21·5 ,,
1800	17·5 ,,	29 ,,

Tracing 47.



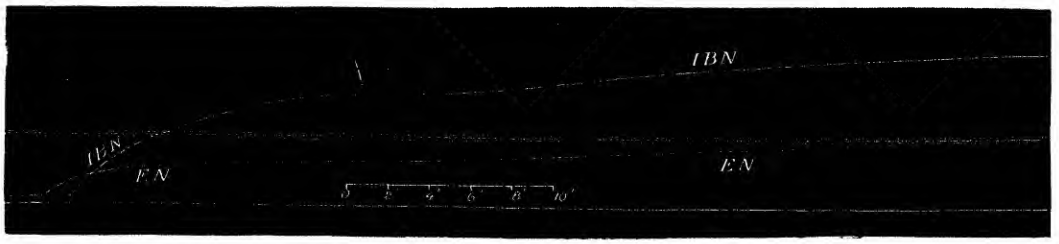
Action of ethyl nitrite on actively contracting muscle. (See protocol.)

(27.7.90.) *Experiment* in which stimulation is made, is taken from a triceps burdened with 10 grms. Axial weight. Lever × 7. Temperature 13°·3 C. Tracing 47.

	Time.	Active contraction on stimulation.	Passive shortening.
	secs.		
Admit $\frac{1}{70}$ cub. centim. (= 0·0127 grm.; NO_2 = 0·0079 grm.) ethyl nitrite to the muscle-chamber	0	22 millims.	
	42	..	Commences
	120	13 ,,	13 millims.
	240	3·5 ,,	23·5 ,,
	360	1 ,,	28 ,,
	495	Ceases	28·5 ,,

As exhibiting the speed of appearance of initial contraction and the extent of the effect produced, the following figures may serve as illustrations. The curve of ethyl nitrite was, however, taken at a lower temperature than that of iso-butyl nitrite. Tracing 48.

Tracing 48.



Contrasted action of ethyl and iso-butyl nitrite on resting muscle. (See protocol.)

Substance.	Dose.	Lever.	Weight.	Temperature.	Initial contraction.	Shortening.					
						5 mins.	10 mins.	20 mins.	40 mins.	80 mins.	160 mins.
			grm.	° C.	secs.	mm.	mm.	mm.	mm.	mm.	mm.
Ethyl nitrite	$\frac{1}{100}$ cub. centim. (= 0·0089 grm.; NO_2=0·00545 grm.)	× 6	7·5	11·5	54	7·5	9·5	10·5	14		
Iso-butyl nitrite	$\frac{1}{100}$ cub. centim. (= 0·0087 grm.; NO_2=0·0038 grm.)	× 6	7·5	12·5	98	17	26	31	39·5		

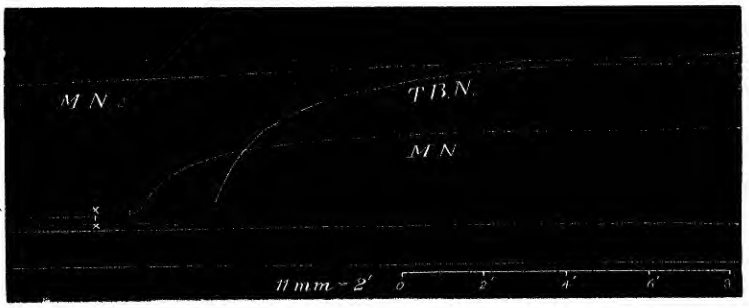
Tracings 31 and 35 also illustrate speed and manner of action of small doses. As regards extent of contraction occasioned, ethyl nitrite is inferior to all the other nitrites excepting methyl; it comes after amyl nitrite in this respect.

Methyl Nitrite.—As already stated, this body was prepared in the gaseous form for

use in bulbs having a measured capacity. These bulbs were filled at a noted temperature and pressure.

Before the experiment commenced, the muscle cylinder was partly filled with salt solution. The bulb was brought into connection with a glass tube situated high up on the side of the cylinder, and to its lower end was attached a rubber tube connecting it with a syringe charged with salt solution. The ends of the bulb were broken within the tubes, and the salt solution allowed to run from the cylinder as the nitrite entered, before the salt solution slowly driven into the bulb from the syringe. By carefully measuring the exact amount of salt solution in the cylinder, a substitution for this by the gas was effected so that the cylinder was practically emptied of solution. The results were very uniform.

Tracing 49.



Contrasted action of methyl and tertiary butyl nitrite on resting muscle. (See protocol.)

Methyl nitrite is the most active of all the nitrites in causing an early initial shortening of the muscle. In from 25 to 50 seconds, according to the dose and temperature, &c., the first indication of rise of the lever is noticed. The substance most nearly approaching it in this respect is the ethyl nitrite, which is, however, distinctly slower. When the contraction has once commenced it progresses rapidly, so that an abrupt rise, reminding one of tertiary amyl and butyl nitrite, is recorded.

Thereafter the rise goes on for a time but it is very gradual. The total shortening produced is less than that occasioned by a similar dose of any nitrite which has been examined under similar conditions. The following experiment will serve to contrast the effect of tertiary amyl nitrite and methyl nitrite. Tracing 49.

Substance.	Dose.	Lever.	Weight.	Temperature.	Time of initial contraction.	Shortening.					
						2 mins.	4 mins.	8 mins.	16 mins.	32 mins.	64 mins.
			grms.	° C.	secs.	mm.	mm.	mm.	mm.	mm.	mm.
Methyl nitrite	4·3 cub. centims. (4·3 cub. centims. of gas = $\frac{1}{82}$ cub. centim. of liquid bulb = 0·0110 grm.; NO_2 = 0·00829 grm.)	× 6	7·5	14	43·5	5·5	8	10	11	11·5	
Tertiary amyl nitrite	$\frac{1}{100}$ cub. centim. (= 0·0089 grm.; NO_2 = 0·0035 grm.)	× 6	7·5	14	140	0	12	18	20	21	

Contrasted with iso-butyl nitrite, the early part of the methyl curve is much more rapid, whilst the gradual development of the butyl effect causes a slower cutting of the methyl curve, but the characteristic rise above it, so that a dose of $\frac{1}{100}$ cub. centim. of the iso-butyl nitrite far exceeds in 10 minutes the effect of a 9·3 cub. centims. bulb of methyl nitrite equal to $\frac{1}{38}$ cub. centim. Tracing 50.

Tracing 50.

Contrasted action of methyl and iso-butyl nitrite on resting muscle. (See protocol.)

Substance.	Dose.	Lever.	Weight.	Temperature.	Time of initial contraction.	Shortening.					
						2 mins.	4 mins.	8 mins.	16 mins.	30 mins.	60 mins.
			grm.	° C.	secs.	mm.	mm.	mm.	mm.	mm.	mm.
Methyl nitrite	9·3 cub. centims. bulb (= 0·0238 grm.; NO_2 = 0·0179 grm.)	× 6	7·5	9·75	43	1·0	14·5	17·5	21	24	29
Iso-butyl nitrite	$\frac{1}{100}$ cub. centim. (= 0·0087 grm.; NO_2 = 0·0038 grm.)	× 6	7·5	9·75	126	0	9·5	20·5	31·5	37·5	52

It will be noticed that the application of the iso-butyl nitrite occurs before that of the methyl nitrite in this curve.

The last measurements which will be given contrast the effect of methyl and ethyl nitrites. A large dose of each substance is employed; a 13 cub. centims. bulb of methyl nitrite (= $\frac{1}{27}$ cub. centim.) and $\frac{1}{30}$ cub. centim. ethyl nitrite respectively.

Substance.	Dose.	Lever.	Weight.	Temperature.	Time of initial contraction.	Shortening.					
						1 min.	2 mins.	4 mins.	8 mins.	16 mins.	30 mins.
			grm.	° F.	secs.	mm.	mm.	mm.	mm.	mm.	mm.
Methyl nitrite	13 cub. centims. bulb (= 0·0291 grm.; NO_2 = 0·0219 grm.)	×11	10	54	35	3·5	8	10	11·5	13·5	18
Ethyl nitrite	$\frac{1}{30}$ cub. centim. (= 0·0296 grm.; NO_2 = 0·0182 grm.)	×11	10	54	48	1	5	14·5	20	24	28·5

Having described in detail the action of the various nitrites respectively upon striated muscular tissue, we can now arrange them in series according to—

(*a*.) Their power of causing shortening of resting muscle—
1. With reference to the extent of this shortening.
2. With regard to the speed of its occurrence.

(*b*.) Their power of modifying the active contraction of muscle subjected to periodic stimulation.

(*a*.1) The order of activity of the nitrites with reference to the extent of muscular shortening produced is as follows:—

(We consider here the shortening occurring in from 15 minutes to 120 minutes after the introduction of nitrite into the muscle chamber, not the shortening occurring sooner, as this must vary with the speed of initial action of the nitrite, and also with the tendency for a maximal effect for a given dose to be rapidly or slowly produced.)

1. Iso-butyl nitrite.
2. Tertiary amyl ,,
3. Secondary butyl ,,
4. ,, propyl ,,
5. Propyl ,,
6. Tertiary butyl ,,
7. Butyl ,,
8. α-Amyl ,,
9. β- ,, ,,
10. Ethyl ,,
11. Methyl ,,

(α.2) SPEED of Occurrence of Shortening.

1. Methyl	nitrite.	
2. Ethyl	,,	
3. Secondary propyl	,,	
4. Tertiary amyl	,,	
5. Primary propyl	,,	} nearly equal.
6. Tertiary butyl	,,	
7. Secondary butyl	,,	
8. α-Amyl	,,	} nearly equal.
9. β- ,,	,,	
10. Butyl	,,	} nearly equal.
11. Iso-butyl	,,	

(b.) The curve uniting the points from which successive contractions ascend is not strictly parallel with the curve of passive contraction of an unstimulated muscle exposed to a similar amount of an individual nitrite, the weight and temperature being equal. The former is modified by the increased tonus, or after-shortening, of those muscle fibres which are still capable of contracting in response to recurring stimulation as well as of those which are passing, or have already passed into rigor. In the other direction, the extending force of the falling weight (the weights were free, *i.e.*, unsupported) after active contraction tends to elongate the muscular tissue.

We do not propose to enter, at the present time, into a consideration of the part which these factors play in modifying the passive shortening of the muscle, inasmuch as it would not aid us in our present endeavour to separate the nitrites from one another. The abolition of active contraction runs so far parallel with the power of individual nitrites to cause passive shortening, terminating in well-marked rigor of resting muscular tissue, that it may be said, in a word, that these conditions, within certain limits, show a parallel progress to one another. When companion muscles are stimulated in an atmosphere containing nitrite vapour, the muscle which shortens the more powerfully ceases to contract sooner in response to stimulation, provided the initial active contraction was equal in the two cases. If this condition was not fulfilled, divergencies from the usual course were from time to time observable; a feebly contracting muscle, tending to "give in," or cease contracting at an earlier phase of shortening than a powerfully reacting muscle. Experiments of this nature were necessarily discarded. The remaining ones permit us to classify the nitrites with reference to their power of abolishing active contraction in the same order as in Table α.1.

It was ascertained that very minute doses of the nitrites, insufficient to cause marked passive shortening, interfered with active contraction, causing the failure of the muscle to respond to stimulation, whilst the companion muscle, in a closed chamber devoid of nitrite vapour, still responded. A comparison of the action of the various

nitrites in this respect, which would have involved an additional series of observations to those already made, was not considered of sufficient importance to be undertaken in connection with the present inquiry.

IX.—Discussion of the Mode of Dependence of Physiological Action on Chemical Constitution.

We now proceed to discuss the mode of dependence of the physiological action of the paraffinic nitrites on their molecular composition and structure.

The different phases of physiological action concerning which we have obtained accurate quantitative data are (1) acceleration of the pulse-rate; (2) reduction of the blood-pressure in respect of (*a*) its extent, and (*b*) its duration; (3) contraction of striated muscular fibre in respect of (*a*) its extent, and (*b*) its rate. The quantitative variations in these effects, which follow from the administration of equal volumes of the various nitrites, have been accurately measured.

Several physical and chemical differences in these bodies must be taken into account in correlating physiological action with chemical constitution, and it will be well to state briefly what these are before the action of each is separately considered.

In the first place it must be pointed out that, since equal volumes of the liquid nitrites, measured at 15° C., have been employed in the physiological experiments, and the relative densities of these liquids are not identical, the equal volumes will not represent exactly equal weights. The nitrites of high molecular weight (butyl, amyl) have slightly smaller relative densities than those of low molecular weight (ethyl, propyl), so that, as the same volume of all the nitrites has been taken, the corresponding weights of the lower nitrites will be greater than those of the nitrites which stand higher in the series. These differences in weight, corresponding to the small volumes used in these experiments ($\frac{1}{30}$th to $\frac{1}{200}$th cub. centim.) are, however, relatively very small, and only affect the quantities used in the fourth or fifth decimal place. Thus, if we calculate the weights corresponding to the $\frac{1}{50}$th cub. centim. of the two nitrites which exhibit the greatest differences in their relative densities, ethyl nitrite and tertiary butyl nitrite, the difference between them only amounts to 0·0006 grm., which represents a smaller volume than it would have been practicable to measure under the circumstances of our experiments. Although these differences are so minute it is worth while to take them into account in calculating the weight of nitroxyl (NO_2) contained in equal volumes of the different nitrites, and for this reason in the record of each experiment the weight corresponding to the volume taken has been given within brackets.

Another difference in physical property to which attention must be paid is that in volatility. Ascending the homologous series from ethyl nitrite to amyl nitrite it is observed that the boiling point of the primary compounds increases by almost exactly

30° C. for each addition of CH_2. The tertiary nitrites boil at lower temperatures than the secondary nitrites and these in their turn at lower temperatures than the corresponding primary compounds. With the exception of methyl nitrite, which is a gas, all the nitrites used are liquids at common temperatures. It is conceivable that the more volatile nitrites might act more rapidly than those which are less volatile, whilst the effect produced by the volatile nitrites might be expected to be more transitory than that of the less volatile, and therefore less diffusible compounds.

All the nitrites examined belong to a homologous series the composition of whose members is representable by the general formula $C_nH_{2n+1}NO_2$ from which it follows that as the series is ascended with increase of molecular weight, the amount of nitroxyl contained in each molecule decreases. This fact has an important bearing on the elucidation of the chemical cause of the physiological action of these bodies. For if their physiological activity is conditioned by the presence of the nitroxyl group then this activity should be most powerfully exerted by those compounds which are richest in this constituent, viz., those of low molecular weight, which stand at the commencement of the series; whereas those nitrites which contain proportionately less nitroxyl, viz., those of high molecular weight, which stand last in the series, should be the weakest in their physiological action. That the presence of the nitroxyl group is the principal cause of the characteristic physiological effects of these compounds there can be no doubt, since the inorganic nitrites (sodium and potassium nitrites) have been observed to give rise to many of the phenomena described in the former part of this paper as arising from the administration of organic nitrites. This being so the question to be elucidated is to what extent, and in what manner, do the different alkyl radicals, which in the organic nitrites are joined to nitroxyl, modify its characteristic action. It may happen that these alkyl radicals act in the same physiological direction as nitroxyl, in which case the difference in the power of the lower and higher members of the series would not be so prominent, and, in the event of the activity of these alkyl radicals becoming greater as the series is ascended, might not even be distinguishable. Unfortunately the physiological action of other salts of these alkyl radicals has not been investigated with any great minuteness, although there is recorded evidence that their hydroxides or alcohols, when administered in small doses, lead to an acceleration of the pulse-rate which is also a prominent feature in the action of the nitrites.

Since the different phases of the physiological action of these organic nitrites vary with an increase in molecular weight, and also with the employment of primary, secondary, or tertiary compounds, it will be necessary to consider the constitutional differences which exist in these compounds, to the influence of which the variations in physiological action must be directly or indirectly due. It will be convenient to point out here once and for all in what these differences consist.

The primary nitrites, both normal and iso-primary, differ from the secondary and tertiary compounds in containing nitroxyl joined to a methylene group (CH_2) and all

these primary compounds therefore contain the complex (CH_2NO_2) united with different alkyl radicals. In the secondary nitrites one atom of hydrogen in this group is replaced by methyl $(CH_3)CH(CH_3)NO_2$ whilst in the tertiary nitrites both the hydrogen atoms are replaced by methyl, and these bodies therefore contain the group $C(CH_3)_2NO_2$.

The relationships subsisting between the members of this homologous series may be represented most conveniently for the purposes of this discussion by considering each compound as the methyl derivative of that standing immediately below it in the series, and from which it may be regarded as formed by the replacement of an atom of hydrogen by methyl (CH_3 or Me). Thus ethyl nitrite ($CH_2(Me)NO_2$) may be looked upon as the methyl derivative of methyl nitrite (CH_3NO_2), the two propyl nitrites (primary and secondary) as the methyl derivatives of ethyl nitrite; if the methyl group takes the place of an atom of hydrogen in the already existing CH_3 group of this compound we have the primary propyl nitrite ($CH_2CH_2(Me)NO_2$), but if it replaces hydrogen in the methylene (CH_2) group, the secondary propyl nitrite $CH(Me)CH_3NO_2$ or $CH(CH_3)_2NO_2$ results. Similarly the four butyl nitrites (primary, iso-primary, secondary, and tertiary), may be regarded as methyl derivatives of the two propyl nitrites. Primary butyl nitrite ($CH_2CH_2CH_2(Me)NO_2$) results from the introduction of the methyl into the already existing methyl group of primary propyl nitrite; if the radical takes the place of hydrogen in one of the methylene groups, but not in that which is attached to nitroxyl, the iso-primary butyl nitrite ($CH_2CH(Me)CH_3NO_2$) is obtained. In the secondary butyl nitrite ($CH(Me)CH_2CH_3NO_2$) the substituted methyl radical occupies the place of an atom of hydrogen in the CH_2NO_2 group of primary propyl nitrite, whilst in the tertiary butyl nitrite ($C(Me)(CH_3)_2NO_2$ or $C(CH_3)_3NO_2$) it takes the place of hydrogen in the $CH\,NO_2$ group of secondary propyl nitrite, and so on.

From this point of view the nitrites with which we have to deal may be systematically arranged as follows, the newly substituted methyl group being represented by the symbol (Me).

Nitrites.	Primary.	Secondary.	Tertiary.
Methyl CH_3NO_2 .	CH_3NO_2	—	—
Ethyl $C_2H_5NO_2$ . .	$CH_2(Me)NO_2$	—	—
Propyl (2) $C_3H_7NO_2$	$CH_2CH_3(Me)NO_2$	$CH(Me)CH_3NO_2$	—
Butyl (4) $C_4H_9NO_2$.	$CH_2CH_2CH_2(Me)NO_2$ (normal) $CH_2CH(Me)CH_3NO_2$ (iso-)	$CH(Me)CH_2CH_3NO_2$	$C(Me)(CH_3)_2NO_2$
Amyl (3) $C_5H_{11}NO_2$	$CH_2CH_2CH(Me)CH_3NO_2$ (α-iso) $CH_2CH(Me)CH_2CH_3NO_2$ (β-iso)*	—	$C(Me)CH_3CH_2CH_3NO_2$

* The physiological action of the α-iso-amyl and β-iso-amyl nitrites is so nearly the same, that in this discussion no distinction will be made between them.

All the nitrites of this series suffer decomposition more or less readily, especially when in contact with dilute acids or alkalies. The principal chemical change consists in hydrolysis of the nitrite into nitrous acid, and the corresponding alcohol, in accordance with the equation $R'NO_2 + H_2O = R'OH + HNO_2$; but a number of secondary changes also take place, most of which originate with an oxidation of the alcohol. The nitrites which stand highest in the series, *i.e.*, those of high molecular weight, are the most readily decomposed, whilst the secondary and tertiary bodies suffer decomposition far more easily than primary compounds; and the iso-primary bodies, apparently, are rather more subject to change than the normal compounds. As will subsequently be pointed out, the readiness with which the nitrites suffer decomposition appears to be closely connected with certain phases of their physiological activity. Having now referred to the most important differences in the chemical properties of these nitrites, whose physiological effects have been investigated, we are in position to discuss the connection subsisting between these two classes of phenomena.

Acceleration of the Pulse-Rate.—The acceleration in the rate of the pulse beat is one of the most remarkable effects resulting from the administration of these compounds, either by inhalation or by intra-vascular injection to animals or to man. There is, however, a very marked variation in the power of the different nitrites in this respect. The numerical order corresponding with the increasing powers of these compounds in accelerating the pulse is as follows.* The nitrites are divided into primary, secondary, and tertiary compounds, and the numbers within brackets refer to the general order of activity.

Primary nitrites.	Secondary nitrites.	Tertiary nitrites.
1. Methyl (1) 2. Ethyl (2) 3. Propyl (3) 4. Butyl (normal) (5) 5. Butyl (iso) (7) 6. Amyl (α and β-iso) (9)	1. Propyl (4) 2. Butyl (6)	1. Butyl (8) 2. Amyl (10)

This order is for the most part the same whether the nitrites are administered by inhalation or by intra-vascular injection, and in all the cases examined, as far as they have been tested, holds good for man, as well as for animals. The acceleration resulting from intra-vascular injection is, however, invariably less than that occasioned by inhalation. The nitrites of low molecular weight possess little or no power of accelerating the pulse, and indeed in some cases actually retard it. The order of physiological activity exactly corresponds with that in which these nitrites stand in the homologous series, that is to say, the physiological activity increases with the molecular weight. Contrasting the action of corresponding primary, secondary, and

* In previous tables in the paper the nitrites are arranged in the reverse order, beginning with the most active.

tertiary compounds, the secondary and tertiary nitrites possess the greatest power, the tertiary amyl nitrite being indeed the most active of all the nitrites examined.

If correction is made for the slightly different densities of the liquid nitrites, equal volumes of which have been administered, and equal weights are calculated, it does not disturb the order, since it would favour the nitrites of high molecular weight which already occupy the leading position. The greater volatility and diffusibility of the lower members evidently does not give them an advantage in connection with the action on the pulse.

This order of physiological activity is not in harmony with the view that the action on the pulse is entirely, or even principally conditioned, by the presence of nitroxyl, indeed, the facts as they stand point to exactly the opposite conclusion. A certain volume of ethyl nitrite, which is with one exception the weakest member of the series, represents twice as great a weight of nitroxyl as the same volume of the most active compound, viz., tertiary amyl nitrite, and in general the physiological activity is inversely as the amount of nitroxyl the compound contains.

When the differences in the chemical constitution of these nitrites are taken into account, we are led to the conclusion that either directly or indirectly the methyl, and not the nitroxyl group is the determining cause of activity, since the successive substitution of methyl, which occurs as the series is ascended, is accompanied by an increase in pulse-accelerating power, whilst this introduction of methyl involves a proportionate decrease in the amount of nitroxyl. The superior activity of secondary and tertiary compounds proves that the physiological effect of the substitution of methyl is greatest when it occurs in the hydrogen of the methylene group, which is in direct union with nitroxyl (CH_2NO_2); that is to say, when the methyl group is joined to the carbon atom which is directly united to nitrogen, as in secondary nitrites, the physiological effect is greater than when the methyl group is attached to any one of the carbon atoms not directly united to nitrogen, and the attachment of two methyl groups to this particular carbon atom, which occurs in tertiary compounds, produces a greater physiological effect than the attachment of only one such group.

The influence of methyl in enhancing the physiological action of these bodies being thus certainly demonstrated, the question arises as to whether this influence is direct or indirect. As evidence that the influence may be in part direct, the similar action of the corresponding alcohols may be mentioned. It appears that in small doses the alcohols lead to an acceleration of the pulse, and that their power in this respect increases as the series is ascended, that is to say, with each addition of methyl. The behaviour of the alcohols has not, however, been investigated sufficiently fully to justify us in accepting any conclusion drawn from an apparent analogy between their action and that of the nitrites, unless it is confirmed by independent evidence. We believe that the data we have recorded put beyond question the conclusion that for the most part the effect produced by the introduction of methyl is an indirect one. The progressive increase in molecular weight, which accompanies the successive introduction

of methyl, causes a gradual decrease in the chemical stability of the nitrites, the higher nitrites being more susceptible to decomposition than those lower in the series. It is this tendency to decompose, which appears to govern the physiological action of these compounds, those bodies which most readily decompose being the most active, and *vice versâ*. The conclusion that the connection between instability and physiological action is a causal one, receives support from the behaviour of corresponding primary, secondary, and tertiary nitrites. The secondary and tertiary bodies are the most active, and are also the most unstable; in fact, on this account it is very difficult to prepare them, and impossible to retain them in a pure state. Here, again, the great increase in physiological power which attends the attachment of one or two methyl groups to the carbon atom directly bound to nitrogen seems to be principally due, not to the direct physiological influence of the substituted methyl group, but to the chemical instability which the introduction of this group confers on the molecule. What the exact nature of the chemical change is which accompanies the manifestation of the physiological action it is impossible to assert for want of experimental data. It may proceed by way of oxidation or of hydrolysis. GAMGEE ('Phil. Trans.,' 1868, 589), who was the first to study the remarkable change in the colour of arterial blood, from bright red to chocolate brown, which is noticed whenever nitrites are administered, has suggested that it is the result of the formation of a combination of the nitrite with the hæmoglobin. The fact that later observers have shown that the actual colour change is due to the production of methæmoglobin, and may be brought about by substances other than nitrites, has caused this suggestion of GAMGEE, which is strongly supported by his experimental data, to be lost sight of. Our own results have led us to believe that the combination of the nitrites with the hæmoglobin, or with some other constituent of the blood, is very probably the first step in the chemical change which unquestionably occurs when a nitrite is brought into contact with the blood or with muscle. Chemical decomposition, however, doubtless very quickly follows this initial combination, especially with the higher and less stable compounds. Preliminary experiments made with the object of tracing the chemical changes which nitrites undergo in the body have proved that these compounds are eliminated in the urine chiefly as nitrate, since more than two-thirds of the total quantity may be recovered from the urine in this form if certain precautions are taken. Thus whilst in the first chemical change the nitrite probably enters into a loose combination, the final chemical result is oxidation, but where this oxidation takes place, and what the preceding chemical changes are, it is impossible at present to say, except that hydrolysis almost certainly precedes the oxidation. In connection with the conclusion that chemical instability is the property which determines the physiological activity of these nitrites in accelerating the pulse, it is interesting to observe that the behaviour of the lower members of the series which do not so readily decompose leads to the suggestion that *per se* the paraffinic nitrites, at any rate when administered in small doses, do not accelerate but actually retard the pulse-

beats, and that acceleration only commences when chemical change has set in. Methyl nitrite, the lowest and most stable member of the series, produces immediately after its administration a great retardation in the beat of the pulse, followed after an interval by a very small acceleration. Ethyl nitrite behaves similarly, the first effect being to retard the pulse-rate, whilst this is followed after a distinct interval by a slight acceleration, greater, however, than that resulting from methyl nitrite. Propyl nitrite produces at first a small retardation, and afterwards a marked acceleration. The nitrites higher in the series than proypl nitrite produce little or no initial retardation, but after the lapse of some seconds considerable acceleration is observed. These peculiarities are quite in harmony with the view expressed above. The action of small quantities of the unaltered nitrites, which is most prominent in the case of the lower stable members, is to retard the pulse; but after a definite interval, when decomposition has commenced, an acceleration more or less rapidly ensues, being most marked in the case of the highest and least stable members of the series.

Reduction of the Blood-Pressure.—In this prominent physiological effect of the administration of the nitrites we have a more complicated problem to unravel than the action on the pulse. It has already been remarked, in the first part of this paper, that evidence has been obtained which goes to show that the pulse acceleration cannot be regarded as wholly due to the fall in blood-pressure, and that the two results must be considered to some extent as distinct.

In discussing the action of the various nitrites on blood-pressure we have to distinguish between the extent of the reduction and the time during which it lasts, since the nitrites which give rise to the greatest fall, are not identical with those whose action is most prolonged.

The following is the order corresponding with the increasing power of the various nitrites with reference to the extent to which they reduce the normal pressure of the blood :—

Primary nitrites.	Secondary nitrites.	Tertiary nitrites.
1. Propyl (1) 2. Ethyl (2) 3. Butyl (3) 4. Methyl (4) 5. Amyl (5) 6. Iso-butyl (7)	1. Propyl (10) 2. Butyl (8)	1. Butyl (9) 2. Amyl (6)

This order is generally the same as that for pulse acceleration. The secondary and tertiary nitrites and, after them, the iso-primary nitrites of amyl and butyl stand highest, and are more active than the normal primary compounds. In general the power of reducing blood-pressure increases with molecular weight, but there are several exceptions to the rule, notably in the case of methyl nitrite, which occupies a higher position as a pressure reducing agent than it does as a pulse accelerator.

If correction is made for the difference in the densities of these liquids the position of some of the nitrites of small molecular weight would probably be lowered, and a nearer approximation obtained to an order corresponding with that of the homologous series.

It is, however, remarkable that in most cases an increase in the quantity of nitrites administered does not lead to the corresponding increase in the reduction of blood-pressure which we should expect, in fact the relatively powerful action of small quantities of these compounds is very extraordinary.

The differences in the boiling-points of the liquids do not seem to exercise any important influence on the extent to which they reduce blood-pressure. Those boiling at lower temperatures do not act more rapidly.

The amount of nitroxyl present in the compound evidently does not here, any more than in the action of the pulse, condition the physiological activity. The tertiary butyl and amyl nitrites, though containing much less nitroxyl than the nitrites of ethyl and propyl, are the most active. With certain exceptions the power of reducing blood-pressure increases with the molecular weight, and, therefore, with the introduction of the methyl group. The conclusion arrived at in connection with the similar though more regular relationship of the methyl radical to the power of accelerating the pulse is evidently also applicable here. The determining cause of the reduction of blood-pressure is the chemical instability of the higher members of the series, and especially of the secondary and tertiary compounds. There is no recorded evidence to show that the increase in activity is the result of the direct physiological influence of the methyl group.

As we know next to nothing about the nature of the chemical changes which accompany the reduction of blood-pressure, it is not possible to discuss this relationship any more fully on its chemical side than was done in connection with pulse acceleration, and for the same reason it is not possible to offer any satisfactory explanation of the irregularities which the table discloses in the behaviour of some of these compounds.

The results taken as the basis of the foregoing discussion of the experiments on blood-pressure were obtained by administering equal volumes of the liquids by inhalation. When these compounds are given by intra-vascular injection they produce a similar effect, and in general there can be no doubt that the action results from the same cause.

As regards duration of the sub-normal pressure the order of increase is as follows :—

Primary nitrites.	Secondary nitrites.	Tertiary nitrites.
1. Propyl (1) 2. Iso-butyl (3) 3. Amyl (4) 4. Butyl (5) 5. Ethyl (9) 6. Methyl (10)	1. Propyl (2) 2. Butyl (6)	1. Butyl (7) 2. Amyl (8)

The relatively small reduction of pressure effected by the primary nitrites of ethyl and methyl lasts longer than that produced by any other nitrite, even by those having the highest molecular weights whose power of reducing pressure is very considerable. In most cases it appears that those nitrites which occasion the most extensive fall in blood-pressure act for the shortest time, and *vice versâ*. The most important exception to this statement is found in the action of primary propyl nitrite which is the weakest member of the series both in respect of the extent to which it reduces blood-pressure and also in the duration of its action. In duration, as well as in extent of reduction, secondary and tertiary nitrites are more powerful than the corresponding primary compounds; secondary propyl nitrite is stronger than primary propyl nitrite, secondary butyl nitrite is stronger than primary butyl nitrite, tertiary butyl nitrite is more active than either the primary or secondary compounds, and tertiary amyl nitrite is more active than iso-primary amyl nitrite.

It does not appear that the correction for the differences in density of the liquid nitrites would materially affect the order given above for equal volumes, since unless the quantity administered is very largely increased, the duration of subnormal pressure is not affected to any great extent.

The difference in the volatility of the various nitrites does not appear to operate in the direction that might be expected, since the action of two of the most volatile and readily diffusible compounds is the most prolonged.

In its relation to molecular composition the greatest duration of subnormal pressure is in general associated with low molecular weight, and, therefore, with those compounds which contain a proportionately large amount of nitroxyl. It is, however, not safe to conclude that the quantity of nitroxyl is the direct and only cause of the permanence of the action on blood-pressure. If it were the direct cause it would follow that a great increase would result from the administration of slightly larger quantities, which is not the case; the duration of subnormal pressure, though greater when larger quantities of the nitrites are administered, falls very far short of being proportionately greater. That the quantity of nitroxyl is not the only factor in the permanence of this physiological effect is clear from the circumstance that, whilst iso-primary amyl nitrite represents almost exactly the same amount of nitroxyl as tertiary amyl nitrite, the latter is much the more powerful compound. The fact that the most volatile and diffusible nitrites (methyl and ethyl nitrites) act for the longest

time, is in accordance with the view that these compounds at first attach themselves to some constituent of blood or muscle, and are, therefore, only slowly eliminated. The nitrites of high molecular weight would less readily enter into combination, and, being more unstable, would be more quickly decomposed ; and thus these effects would last for a shorter time than those of the more stable compounds of lower molecular weight.

It is not possible in the present state of our knowledge to offer a complete chemical explanation of the peculiarities in the behaviour of these nitrites in reducing blood-pressure. There can, however, be no doubt that whilst the causes which lead to the acceleration of the pulse and the reduction of pressure are essentially the same, those which control the duration of subnormal pressure are distinct ; the first-mentioned effects are associated with molecular instability, whilst the latter effect, in its intensest form, is produced by the most stable compounds of the series.

Contraction of Striated Muscular Fibre.—In examining the action of equal volumes of the nitrites on striated muscle, there were observed to be two distinct aspects of this action, which invariably leads to passive muscular contraction. One relates to the extent to which the contraction takes place, and the other to the rapidity with which it occurs. These two manifestations of power are not associated with the same nitrites. Considering first the extent of the contraction, the order representing the increasing power of the various nitrites in this respect is as follows :—

Primary nitrites.	Secondary nitrites.	Tertiary nitrites.
1. Methyl (1) 2. Ethyl (2) 3. Amyl (3) 4. Butyl (4) 5. Propyl (6) 6. Iso-butyl (10)	1. Propyl (7) 2. Butyl (8)	1. Butyl (5) 2. Amyl (9)

This order presents many similarities with that for extent of reduction of blood-pressure. The secondary and tertiary nitrites are again the most active compounds with the exception of iso-butyl nitrite, which acts more powerfully than any other member of the series. The nitrites of methyl and ethyl are the least efficient in producing muscular contraction.

It does not appear that the order for equal weights of the nitrites would differ in any important respect from that given above for equal volumes. It is difficult to determine how far the differences in the volatility of the various nitrites are connected with the differences in this physiological action. The two most volatile compounds, methyl and ethyl nitrites, are certainly the weakest, whilst iso-butyl nitrite, which is one of the least volatile compounds, is the strongest in its action. On the other hand,

the more volatile propyl nitrites are far more active than the much less volatile iso-primary amyl nitrite, which is one of the weakest members of the series. It is clear that volatility is not the most important of the factors which lead to the modification in physiological action. Although there are certain well marked irregularities in the order, if we have regard to the strongest nitrites, viz., those of iso-butyl, tertiary amyl, and secondary butyl, and to the weakest compounds, viz., the nitrites of methyl and ethyl, it appears that, for the most part, the power of contracting muscular fibre is associated with high molecular weight, and is not conditioned by the quantity of nitroxyl which the nitrite contains.

Iso-butyl nitrite, the strongest member of the series, represents less than half the quantity of nitroxyl contained in an equal weight of methyl nitrite, which is the weakest of all the compounds. This fact, taken in conjunction with the high place occupied by the secondary and tertiary compounds, points to the conclusion that chemical instability is here again the principal determining condition of physiological activity.

In relation to the rapidity with which muscular contraction is effected as distinguished from its extent, quite different nitrites prove themselves to be the most efficient. The order in which the nitrites are arranged, according to the increasing rate at which they produce muscular contraction, is as follows :—

Primary nitrites.	Secondary nitrites.	Tertiary nitrites.
1. Iso-butyl (1) 2. Butyl (2) 3. Amyl (3) 4. Propyl (6) 5. Ethyl (9) 6. Methyl (10)	1. Butyl (4) 2. Propyl (8)	1. Butyl (5) 2. Amyl (7)

This order shows some irregularities, but, as far as the quickest and slowest acting nitrites are concerned, it is exactly the reverse of that representing the extent to which contraction is brought about. Iso-butyl nitrite, which causes a greater muscular contraction than any other nitrite, is the slowest in acting, whilst the nitrites of methyl and ethyl, which give rise to the least considerable contraction, are quickest in their action. Among the exceptions attention must be drawn to the remarkable position occupied by the secondary and tertiary nitrites, which is but very slightly inferior to that which they hold in respect to extent of contraction; in all cases the secondary compounds act quicker than the corresponding primary compounds; secondary propyl and butyl nitrites start the contraction before primary propyl and butyl nitrites, whilst tertiary amyl nitrite acts considerably quicker than the iso-primary compound.

The respective positions of these nitrites would not be materially altered if the order were taken for equal weights instead of equal volumes.

The more volatile compounds in many instances act most rapidly, *e.g.*, methyl and ethyl nitrites; but there are numerous exceptions, whilst the differences in the boiling-points of iso-primary and tertiary nitrites, and of iso-butyl nitrite and secondary and tertiary butyl nitrites, are too small to account for the far greater activity of the secondary and tertiary compounds.

In the case of the three most active primary nitrites, viz., those of propyl, ethyl, and methyl, the order of their activity is the reverse of the homologous order, and is therefore inversely as their molecular weights. The three primary nitrites which act most slowly are those of high molecular weight, viz., iso-butyl, butyl, and amyl nitrites. It therefore appears that, as far as the primary compounds are concerned, speed of action is associated with low molecular weight, and therefore with a large proportion of nitroxyl. No doubt the greater volatility which accompanies low molecular weight may also assist the rapid action of these nitrites.

A study of the behaviour of the secondary and tertiary nitrites leads to the conclusion that in these compounds the two factors of low molecular weight, or large nitroxyl content, and volatility, are not alone sufficient to account for the presence of these compounds among the more active members of the series. Between corresponding primary and secondary nitrites there is a considerable difference in speed of action, although there is no difference in molecular weight, and relatively only a small variation in boiling-point. The greater activity of the secondary and tertiary compounds must therefore be attributed to peculiarities in their constitution. These bodies differ from the primary compounds in containing one or two methyl groups attached to the carbon atom which is combined with nitroxyl. It may safely be concluded that the superior activity is not the result of the direct physiological influence of the methyl groups, but to the chemical instability induced by their presence in this part of the molecule, which causes these compounds to be the most readily decomposed of all the nitrites of this series.

We find then, in respect of the speed with which muscular contraction occurs, that first the primary nitrites of low molecular weight, and then the secondary and tertiary nitrites of high molecular weight, are the most active members of the series, whilst the primary nitrites of high molecular weight stand last, in being the slowest in starting muscular contraction. The question at once suggests itself as to why these two widely separated sections of the series should correspond in the rapidity of their physiological action. It has already been pointed out, in connection with the action on blood-pressure, that all the nitrites probably act in the first instance by entering into a loose combination with one of the constituents of the blood, and that the nitrites of low molecular weight no doubt do so the most readily. The results we have obtained with muscle point to a similar conclusion. If the nitrites combine with one of the constituents of muscle, those of low molecular weight entering more readily into combination than those of high molecular weight, the difference in the speed with which the various primary nitrites act becomes, at least, intelligible. As regards the

behaviour of the secondary and tertiary compounds, it is highly probable that, on account of their great instability, they would at once undergo hydrolysis on coming into contact with the acid of actively contracting muscle, and that the separated nitrous acid would then immediately react. The slowness with which the nitrites of high molecular weight act may be ascribed to the circumstances that these bodies enter much less readily into combination, and are far more stable than the secondary and tertiary compounds. The weak chemical union between the nitrites and certain constituents of blood and muscle, of which their physiological action affords indications, although substantiated to some extent as regards the blood by the experiments of GAMGEE, requires detailed chemical study with respect to the nature of the compound, as well as to its modes of decomposition.

In conclusion, the following are the principal facts which have been established with reference to the connection between the various phases of the physiological action of these nitrites and their chemical constitution.

In respect of all phases of the physiological action, the secondary and tertiary nitrites are more active than the corresponding primary compounds. This is to be chiefly attributed, not to the direct physiological effect of the secondary and tertiary groups, but to the great facility with which these compounds suffer decomposition.

In respect of the acceleration of the pulse, the power of the nitrites varies directly as their molecular weights, and they therefore fall into an order identical with that of the homologous series. This same relationship, increase of activity corresponding with rise in molecular weight, may also be traced, though less uniformly, in their power of reducing blood-pressure and of inducing muscular contraction.

This order appears to be the result, not so much of the direct influence of the substituted methyl groups, as of the increased chemical instability which their substitution confers on the higher members of the series.

In respect of the duration of sub-normal pressure, as well as of the rapidity with which muscular contraction ensues, the activity of the nitrites is expressed by an order which is for the most part the reverse of that representing their power in accelerating the pulse, reducing blood-pressure, and contracting muscular fibre, this order being in general contrary to that of the homologous series. In these respects the more volatile nitrites of low molecular weight, and containing, therefore, relatively more nitroxyl, are the most active. It is probable that these simple nitrites more readily attach themselves to constituents of blood and muscle, and thus act more quickly than the higher compounds in inducing muscular contraction, whilst their greater stability causes their effect, *i.e.*, reduction of blood-pressure, to endure for a greater length of time than that of the higher and more easily decomposed bodies.

It is obvious that these results have an important bearing on the therapeutic employment of the nitrites, which in recent years has become more and more extensive. We propose elsewhere to consider what the outcome of this investigation is for practical medicine.